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THE DIAGNOSIS AND PATHOLOGIC PHYSIOLOGY OF ARTERIOVENOUS ANEURYSM *

C F HOOVER, MD, AND A J BEAMS, MD
CLEVELAND

When the systemic arteriovenous circulation is short-circuited by a fistulous communication of sufficient size, symptoms develop so closely simulating those of myocardial decompensation that it may be difficult to evaluate the part contributed to the circulatory defect by the arteriovenous communication. In fact, the increased burden on the heart due to short-circuiting the flow of blood may in time produce genuine myocardial decompensation. The difficulties of diagnosis are still further complicated by the need of determining whether the arteriovenous communication is the sole cause of circulatory symptoms or only a contributory factor in the presence of cardiac disease. Obviously, if all the symptoms are due to arteriovenous fistula, the proper treatment is to close the opening. If the fistula is only a factor of minor importance, the operative procedure may be contraindicated. In the first case we have to report, the cardiac symptoms were so pronounced that a large number of physicians and surgeons advised against surgical procedure, believing the arteriovenous fistula to be of minor importance and the cardiac disease to be the chief cause of the existing venous stasis, chylous ascites and edema.

We find nowhere in medical literature a discussion of the hydraulics of arterial blood flow in arteriovenous fistula, nor any attempt to differentiate between cardiac enlargement caused by arteriovenous openings and that caused by primary disease of the myocardium. These questions must be unequivocally answered before a patient can be given sound advice on the question of operation. When the fistula is in a location that is under digital control, as in a fistula between the femoral artery and vein, it is a perfectly simple matter to compress the artery and determine how the hydraulics of the circulation are affected by eliminating the fistula from the circulation. When, however, the fistula is beyond manual control, as in the root of the neck or intra-thoracic or intra-abdominal, the problem of diagnosis becomes much more difficult.

* From the Medical Department, Western Reserve School of Medicine, Lakeside Hospital

We shall first describe two patients with arteriovenous fistula in the femoral vessels. In one patient the leak could be readily shunted out by compression of the femoral artery at Poupart's ligament, but in the other case the patient had so much edema and so much pain that he could not tolerate digital pressure on the femoral vessels, nor would he tolerate a ligature about the thigh. This was probably the reason that so many physicians had failed to evaluate the fistula in this man's circulatory symptoms.

REPORTS OF CASES

CASE 1—History—A young man, aged 32, who was admitted to the Lakeside Hospital on Nov 29, 1920, had received a rifle bullet through the right thigh at the lower end of Hunter's canal, two years and two months before, while serving in a mortar battery with the army in France. According to the patient's history, he had no fever or any evidence of infection of his wound. About two weeks before he got out of bed, which was about two and a half months after receiving the wound, he observed that his right thigh and leg were swollen and decidedly larger than the left. When walking on crutches, he stepped on the right foot of the wounded side and held his left foot off the ground on account of a superficial wound in the left knee received at the same time as the wound in the right thigh. He observed that he was short of breath and began to have signs of fulness in the abdomen. He was then put to bed again and on examination was found to have free fluid in the abdominal cavity. Two weeks later his abdomen was tapped to relieve the ascitic accumulation. Within the following two years the abdomen was tapped forty times for the relief of ascites.

Examination—When the patient came to the hospital he was able to walk by the aid of a crutch and a cane. The abdomen was greatly distended, and his thorax, extremities and face were emaciated. He seemed to suffer more from exhaustion than from air hunger. Although his ability to get about was limited, he did not cough or exhibit the symptoms of a patient suffering from a high degree of stasis in the pulmonary circulation. Physical examination revealed the apex of the heart at the fifth intercostal space, two thirds of the way to the anterior axillary line from the left midclavicular line. The impulse of the right ventricle was strong, and there were a distinct systolic impulse and a diastolic impact over its conus arteriosus. There was not a clear differentiation between the areas of impulse, but the left ventricular impulse could be differentiated from the right. The precordial area of dulness did not extend beyond the right border of the sternum in the third and fourth interspace. During inspiration the inner half of the left costal margin was diminished in its lateral movement, but the inner portion of the right costal margin moved readily away from the median line. The outer parts of both costal margins moved symmetrically outward during inspiration. The external and internal jugular veins were distended and under considerable pressure. When he was lying with his hands at his side, a distinct centrifugal systolic pulse was visible in the veins of the hands, and the right hand had to be lifted at least 12 inches above the level of the heart before the veins collapsed. The liver was plainly palpable four finger-breadths below the costal margin in the right nipple line. There was a strong systolic pulsation of the liver, which was synchronous with the pulse in the carotid artery; it was so strong that after the ascitic fluid was removed the pulsation of the liver caused a lateral thrust of the ribs on the right side that dragged the entire thorax to the right. With each cardiac systole the lower right ribs were thrust so far in a lateral direction that the borders of the left ribs were drawn toward the right. The

femoral vein on the right side was greatly distended, and the same kind of systolic pulse was visible as in the jugular veins, bulbus venosus and liver. At the lower end of Hunter's canal there was a strong thrill, which was palpable from that position as far upward as Poupart's ligament. Over this entire distance there was a loud systolic murmur, but below the origin of the thrill on the right side there was no murmur audible and no palpable thrill. The pulse in the dorsalis pedis artery was not palpable on either foot, but the posterior tibial pulse on both sides was distinctly palpable. The right thigh and leg were edematous, and there was also slight edema of the left leg and ankle.

A 6 foot (182.8 cm) roentgenogram of the heart showed a globular enlargement. The contour revealed an enlargement of the right ventricle as well as of the left, but showed no evidences of distention of the right auricle to the right of the sternum. When synchronous tracings of the pulse in the bulbus venosus and in the femoral vein of the right side were taken, there was no evidence of an auricular pulse. The pulse was purely systolic in time, and the jugular pulse preceded that of the femoral by one tenth second, so that so far as pulsation of the liver, jugular vein and femoral vein were concerned, the patient evidently had a tricuspid insufficiency and the venous pulsations might be cardiac in origin or might originate from the arteriovenous opening. There were several reasons, however, for believing that the cardiac involvement was secondary to the arteriovenous fistula, and that all the venous phenomena originated from the direct arterial communication and not from cardiac decompensation.

The first reason was that the right auricle was not enlarged. If the venous phenomena at the bulbus venosus and in the liver were secondary to tricuspid insufficiency, there must be an enlarged right auricle, and therefore the fact that there was no evidence of flattening of the subcardial diaphragm at the right of the median line gave rise to the suspicion that the right auricle was not enlarged. Percussion, the fluoroscope and the roentgenogram all confirmed this finding. Moreover, the contour of the heart indicated that the right and left ventricles were equally involved and that their enlargement was due to a common cause. That it could not be from a decompensated left ventricle was suggested by the fact that the patient had a lung capacity of 2,500 c.c. when his expected vital capacity was not above 3,500 c.c. Had all the venous stasis been in consequence of a decompensation of the left ventricle, he would have had pronounced lung rigidity with a great reduction in his vital capacity. Under such circumstances, we should have expected the vital capacity to be reduced to about 1,500 c.c. or even 1,200 c.c.

Operation and Course.—As above stated, the patient would not tolerate sufficient pressure over the region of the femoral artery to shut out the arteriovenous leak. So in anticipation of an operation we could prognosticate only on the basis of the physical examination, but these two points—lack of evidence of stasis in the pulmonary circulation and of ectasis of the right auricle—were sufficient for advising operative procedure. Up to this time surgery had not been advised because the patient was believed to have a primary cardiac disease, to substantiate this interpretation, a positive Wassermann reaction on the blood had finally been procured after four trials, and this test had determined his physicians not to operate but to have the patient treated for syphilitic myocarditis.

On Dec. 5, 1920, we removed 11 liters of ascitic fluid by paracentesis. The fluid was milky in appearance and did not clarify by centrifugation. There were only 135 cells per cubic millimeter, and the amount of albumin, although not quantitatively determined, was smaller than that usually found in pure transudates. Although the fluid did not clarify by contact with ether, Dr. Blankenhorn was able to recover fat in considerable amounts by extraction with petroleum ether in a reflux condenser, and further studies of this fluid, reported elsewhere,

by Dr Blankenhorn,¹ proved its turbidity to be caused by fat in a finely divided emulsion. On the day after the ascitic fluid was removed, the patient was operated on, and there was no reaccumulation.

On Dec 6, 1920, Dr Crile operated on the patient under local anesthesia with nitrous oxide in small amounts. The patient was conscious during most of the operation. The vein and artery at the site of the communication were freely opened. On the inner surface of the artery, in an area 4 by 2 cm, there were about ten small sinuses plainly visible. The collected area of the lumina of all these sinuses, which presented a sievelike appearance, was not in excess of the cross section of the artery. This sievelike area was not removed, but was separated from the neighboring structures by deep ligatures on all four sides.

Directly after the operation it was quite apparent that there had been no primary heart disease and that all the circulatory symptoms had been caused by the arteriovenous fistula. The character of the heart impulse was immediately changed. Although the area of precordial dulness was not lessened, the systolic impulse and diastolic impact over the conus arteriosus of the right ventricle were no longer perceptible. Only the apex impulse was palpable. The contact of the cardiac impulse with the anterior chest wall was diminished in its vigor. One gained the impression that the heart was less globular and the right ventricle smaller, although the location of the apex of the left ventricle was unchanged and the right border of the heart was still at the right sternal border. The large veins were no longer distended, and the centrifugal systolic venous pulse in the jugular vein was replaced by a presystolic centrifugal wave. The hepatic pulse ceased, and the lower border of the liver was slightly below the costal border in the right nipple line. Its consistency was somewhat in excess of normal, and its edge slightly rounded—not so sharp as in hepatic cirrhosis. The impression received from palpating the liver before and after the operation was that the great engorgement within the hepatic veins was allayed but that the edema of the liver persisted. However, within a few days after the operation the liver was no longer palpable, and its percussion boundaries were quite normal.

There were several preoperative and postoperative observations that were interesting. For instance, before the operation the minute volume flow through the right foot (the affected side) was 116 gm per 100 cc of foot volume, as measured by Stewart's method, and through the left foot it was 3 gm per 100 cc, but one month after the operation the same method gave an equal volume flow on the two sides, namely, 18 gm per 100 cc of foot, which is within the normal limits. Before the operation there was marked retention of body fluids, only about half the intake of fluids being eliminated by the kidney, although the phthalein kidney test gave a normal result. The urine at this time contained a trace of albumin and a few hyaline and granular casts. After the operation there was no retention of body fluids, and the urine became normal. The vital capacity of the lungs also became normal, being increased from 2,500 to 3,500 cc. This increase in pulmonary extensibility was more apparent than real. It was in all probability unchanged, for the patient's muscular vigor was so much improved by the closure of the arteriovenous fistula that this alone could account for the apparent increase in lung capacity.

Besides the modification in size of the heart and the disappearance of venous engorgement, the most striking and interesting change was in the character of the arterial pulse. Before the operation the pulse was monocratic and had an extent and celerity in the anacrotus and catacrotus that were suggestive of aortic insufficiency. The arterial pressure measured systolic, 115, diastolic, 65. After the operation the pulse had a smaller excursion and the pressure measured

¹ Blankenhorn, M A. Chylous and Pseudochylous Effusions. A Report of Seven Cases, Arch Int Med 32:129 (July) 1923. The Causes of Turbidity in Milky Ascitic Fluids, *ibid*, p 140.

systolic, 145, diastolic, 95. This was a striking change in the systolic and diastolic pressure with the pulse pressure unchanged, and as we shall later show it occurs only in arteriovenous fistula. All other cardiovascular diseases that modify arterial pressures alter the pulse pressure.

By the latter part of February, eight weeks after the operation, the patient was discharged in perfect health. The roentgenograms of the heart taken before and after operation show a marked diminution in the size of the heart (Fig. 1, A and B). All the cardiovascular and respiratory signs were perfectly normal. The liver had a normal conformation, size and consistency. The urine was normal and the blood flow in the feet was the same.

CASE 2—History.—An Italian woman, aged 58, was admitted to Lakeside Hospital in April, 1921, complaining of shortness of breath and abdominal pain. Four years before entering the hospital she had been wounded by a rifle bullet in the upper right thigh. She was confined to her bed for eighteen days. After recovery from her wound she noticed a pulsation at the lower end of Scarpa's triangle. A year later there was dyspnea on slight exertion, and the ability to exercise grew gradually less.

Examination.—The patient had a well pronounced cardiovascular disease, as shown by the cardiac enlargement and an arterial pressure of systolic, 210, diastolic, 110. In the jugular vein and bulbus venosus there was a systolic centrifugal pulse. The liver was at the level of the umbilicus in the mid-

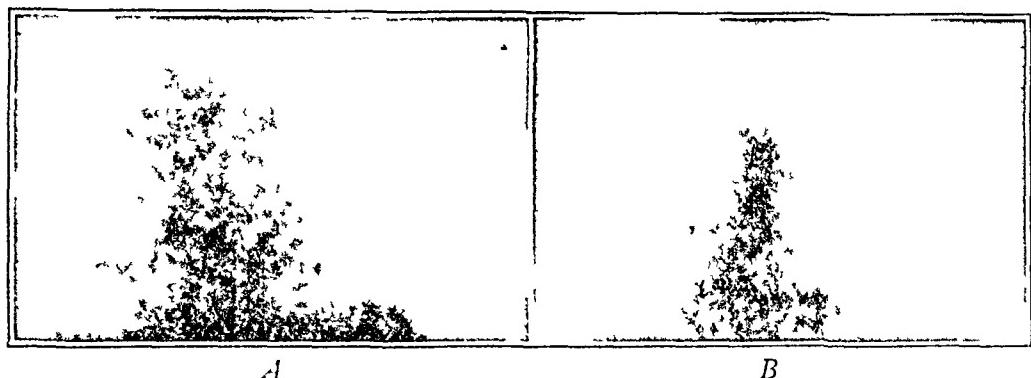


Fig. 1.—A is a 6 foot roentgenogram of Case I before operation, B, a 6 foot roentgenogram of the same patient one month after closure of the arteriovenous fistula.

clavicular line and revealed a pronounced systolic pulse that was synchronous with that in the bulbus venosus. The contour of the heart was globular, although the differentiation between the areas of the left and the right ventricular impulses was more clearly defined than in the first patient. It was noticed, however, that although there was a pronounced hepatic pulse, the right boundary of precordial dulness did not extend beyond the right border of the sternum. The subcardial diaphragm was not flattened at the right of the median line, but it was depressed at the left, as shown by the inspiratory excursions of the costal borders. The inner half of the left border did not move outward during inspiration, but the outer half moved strongly laterad, as did the entire right costal margin.

There were no evidences of stasis in the pulmonary circulation. Four centimeters below Poupart's ligament there was an intense systolic thrill and loud systolic murmur, which was audible during the entire cardiac cycle, but which was greatly accentuated with the expulsive phase of the left ventricle. Although the femoral vein was enlarged, there was no edema of the thigh or leg of the affected side. When the femoral artery was obliterated at Poupart's ligament by digital compression, there followed some striking alterations in

the arterial pressure and character of the pulse. The systolic and diastolic blood pressures both rose 40 mm of mercury, but the pulse pressure remained the same. Before compression of the femoral artery the pressure measured in either arm was systolic, 210, diastolic, 110, and during compression it was systolic, 250, diastolic, 150. When the arteriovenous leak was eliminated, the excursion of the radial and dorsalis pedis arteries was distinctly lessened, as perceived both by touch and by sight. With the arteriovenous leak, the pulse excursion had a range and celerity suggestive of insufficiency of the aortic valves or sclerosis of the aorta. When the arteriovenous leak was eliminated the pulse instantly assumed the character of pulsus durans, which is so marked in the Gull and Sutton variety of arterial sclerosis. The excursion of the artery was lessened, and an interruption high in the catacrotus was plainly visible and palpable in the dorsalis pedis, radial and brachial arteries. This alteration was clearly due to elimination of the systolic and diastolic leak from the femoral artery into the femoral vein. The systolic pulse in the jugular vein was replaced by a presystolic centrifugal pulse, which was plainly auricular in origin. The hepatic pulse ceased with elimination of the arteriovenous leak, and the size of the liver perceptibly diminished.

These changes in the arterial pulse are plainly shown in a tracing made from the radial artery, as seen in Figure 2. At X, the femoral artery above the

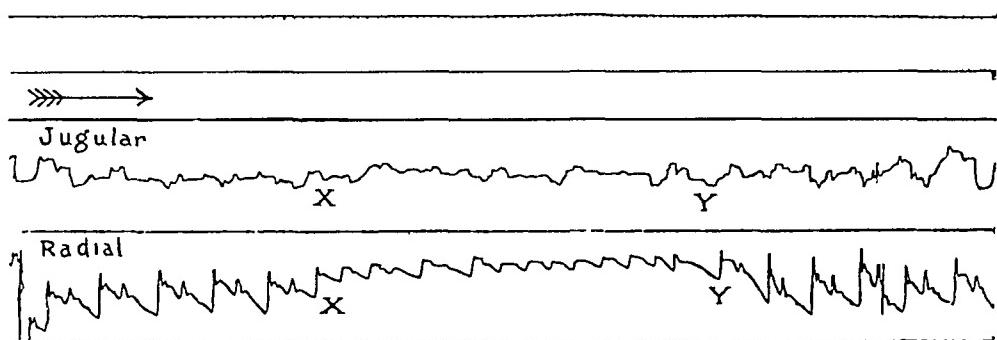


Fig. 2.—This tracing was made by the polysphygmograph from the jugular vein and radial artery of Case II. The running of the sphygmograph was not interrupted at any time in the tracing. The femoral artery above the arteriovenous fistula was compressed at the end of the diastole. Note the instant rise of the minimum diastolic descent with the recording needle. At Y, the artery was released, and immediately there was instant return to the original type of pulse.

fistula was compressed at the end of the cardiac diastole. Instantly the tracing rose to the same height as before compression, but the catacrotus descended only one third as far. The force of the spring that drove the pelote downward so as to register a downward excursion of the needle of 8 mm now drove the needle downward only 3 mm. This was of course due to the increased filling of the artery and the rise of 40 mm of mercury in the diastolic pressure. As the sphygmograph registers only the excursion of the arterial wall, with the stiffening of the arterial system the excursion of the wall is much diminished. At Y, the compression finger was lifted, and instantly the original arterial excursion was resumed. The pulse rate was distinctly increased when the leak was eliminated and not slowed as reported by other observers. The time marker shows no interruption in the tracing.

An operation was not advised in this patient because she had a severe cardiovascular and renal disease which forbade any promise of restoration to health after closure of the arteriovenous leak.

COMMENT

In the second patient the arteriovenous leak was not so large as in the first, but the hydraulics of the blood flow were affected exactly the same in both though in different degrees. In the second patient the significance of the arteriovenous leak was easily determined by compression of the femoral artery above the fistula.

In these two cases there are two demonstrable effects on the circulation that characterize the lesion and also enable the clinician to evaluate the burden added to the heart by the arterial leak. When there is a central leak, that is, of the aortic valves, the severity of the leak is clinically estimated by enlargement of the left ventricle and increase of the pulse pressure. If the diastolic pressure is lowered, there must be a compensatory rise of the systolic pressure to maintain a normal minute volume flow of blood. The left ventricle enlarges to accommodate a compensatory diastolic filling of its chamber. The leak, however, under these circumstances is purely diastolic. If there is a leak distal to the aortic valves, there will of necessity be an enlargement of all the chambers of the heart if the minute volume flow of blood is to be maintained. On the central side of the leak there must be an increased volume flow if the normal flow is maintained in all the distal parts. If 100 cc be the normal output of a left ventricle and an aortic diastolic leak of 20 cc be imposed, then the rate remaining the same, the systolic output of the ventricle must become 120 cc, but only the left ventricle need enlarge to meet this compensatory measure. If the leak of 20 cc during the entire cardiac cycle occurs distally to the aortic valves, not only will there be required a compensatory dilatation of the left ventricle, but the right ventricle will have to meet an equal dilatation, an equal measure of dilatation on the part of the auricles, however, is for obvious reasons not required. The same kind of cardiac enlargement will be needed as occurs in other diseases attended with an increased minute volume flow through the heart. In acute exophthalmic goiter and severe chlorosis, the cavities of the ventricles enlarge, but the enlargement is compensatory, cardiectasis does not occur as in myocardial decompensation, and there is no demonstrable enlargement of the right auricle to the right of the sternum. Enlargement of the precordial area of dulness to the right of the sternum is always due either to ectasis of the right auricle or to an enlarged pericardial sac. The atrioventricular sulcus of the right side of the heart follows closely the right border of the sternum from the third to the fifth intercostal space. When the right ventricle enlarges, its base is not dislocated to the right, but its boundaries move upward to the left in the line of the conus arteriosus and laterally to it, and also downward to the left. When there is ectasis of the right

ventricle and auricle from myocardial decompensation, the subcardial diaphragm to the right of the median line is flattened, and the inner half of the right costal margin is restrained in its lateral movement during inspiration. In severe cases, it may be drawn mediad. When, however, the cardiac enlargement is compensatory for an increased volume flow of blood, as occurs in exophthalmic goiter or in arteriovenous fistula, the subcardial diaphragm is not flattened, the heart seems to be erect, and although enlarged it does not encroach on the phrenic arch.

The absence of enlargement of the right auricle is the most important sign in arteriovenous fistula when the volume of the leak is sufficient to cause a systolic liver pulse, for when an hepatic pulse is due to cardiac decompensation, the subcardial diaphragm at the right of the median line is flattened so that the inner half of the right costal border is either restrained in its laterad movement or drawn toward the median line in inspiration. This sign is the key to differential diagnosis when the leak is not under command of the fingers, for a globular enlargement of the heart, attended with a systolic centrifugal pulse in the veins and a strong hepatic pulse, is likely to be disposed of unquestioningly as venous stasis from cardiac decompensation. When the arteriovenous fistula is under digital command, it is an obvious and simple procedure to demonstrate the degree of arterial leak. If elimination of the leak does not modify the systolic and diastolic pressure, the arteriovenous fistula can have no significance for the systemic circulation. The change in blood pressure without change in the pulse pressure occurs only in this affection. All other sources of changes in blood pressure alter the pulse pressure. This is true in disease of the aortic valve and also when the output of the heart is increased or diminished if the peripheral resistance changes or remains the same.

Should a patient have arterial hypertonus with a pressure of systolic 250, diastolic 150, and the vasomotor tone be relaxed so that the systolic pressure is lowered to 210, the diastolic pressure will not be lowered an equal amount. The diastolic pressure may drop to 125 or 120, but it will not come down to 110, as occurred in our second patient when the arteriovenous leak was reopened after it had been eliminated by digital compression.

PATHOLOGIC PHYSIOLOGY OF ARTERIOVENOUS FISTULA

There were several considerations in these cases that demanded experimental confirmation and further clarification. The essential points we wished to study were the changes in arterial pressure without change of pulse pressure, enlargement of both ventricles without ectasis of the auricles, and hepatic pulsation.

We soon found that anastomoses between normal vessels and fistulas between arteries and veins resulting from trauma gave different results. In neither of our two patients with femoral arteriovenous fistula could the leak have exceeded that of the cross section of a femoral artery, but the arterial and venous pressures were much more affected in our patients than in our experimental animals even when the proportionate arteriovenous anastomoses implicated a larger vascular lumen. In the first of our two patients, the arterial pressure was systolic 115, and diastolic 65 before the leak was closed and systolic 145, and diastolic 95 after the leak was closed, and in the second patient it was systolic 210 and diastolic 110 before and systolic 250 and diastolic 150 afterward. The soldier had a much larger leak than the woman, although his arterial pressure was raised 10 mm of mercury less. The woman had severe arterial sclerosis, so that the stoppage of her smaller leak raised the pressure more than did the stoppage of the larger one in the man.

To reproduce these results in animals we anastomosed both carotid arteries of a dog with their adjacent external jugular veins, with the expectation that the consequent arteriovenous leak would proportionately equal or exceed that of our patients. With the aid of our surgical colleague, Dr. Frank Gibson, such anastomoses were made in May, 1922. By the middle of the following November, the dog showed no signs of venous stasis, and roentgenograms of the dog's heart made each month showed no appreciable alteration in the size of the heart. The dog was killed after an interval of six months, and the arteriovenous communications were perfectly clear, without obstructing thrombi in either vein or artery, and had a circumference of 7 mm on each side. During life there were a strongly palpable thrill and a loud murmur over each opening, and if the lumina of the cut ends of the carotids had not been greatly diminished by vasoconstriction, the circulatory changes in our first patient would have been reproduced, as the dog's arteriovenous communication at necropsy was proportionately much larger than our patient could possibly have had. We sought to remedy this constriction in the dog by dissecting off the adventitia from the anastomosed arteries, but the thrombi in the veins at the points of anastomosis defeated the purpose of the experiment. When the dog's carotid-jugular anastomoses were freely opened, the character of the femoral pulse was perceptibly modified by alternately closing and releasing the carotids, but the palpable changes in the character of the pulse were not so pronounced as in either of the two patients with unilateral fistula in their femoral vessels.

We then tried anastomosing one common carotid artery of a dog with its neighboring external jugular vein so that the proximal end of the artery opened freely into the vein. An arteriovenous leak as

great as in either of the patients above described might have been expected, but the results were disappointing. After the carotid-jugular communication was established, the palpable thrill and murmur indicated a large leak, and by palpating the femoral artery while the arteriovenous opening was alternately closed and opened, the change in the character of the femoral pulse was plainly perceptible to the palpating finger. When the arteriovenous communication was open, the excursion of the femoral artery partook of the celer character, and when it was closed the artery had less excursion. When a cannula connected with a mercury manometer was inserted in the central end of the femoral artery, the changes in pressure were found to be considerably less than one would expect from the thrill and murmur and the palpable and

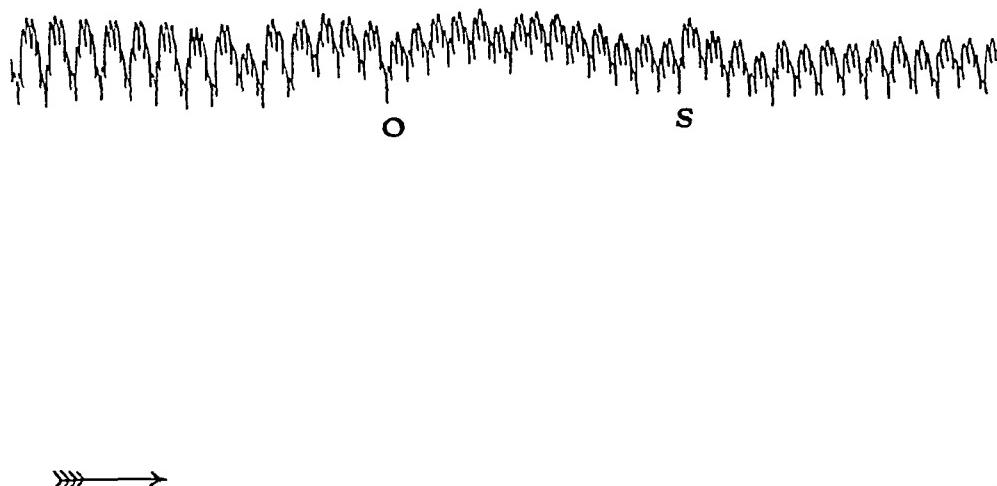


Fig 3.—The tracing is from the femoral artery by means of a U mercury manometer. At O, the arteriovenous communication between the carotid and the external jugular was opened. At S it was closed. The changes in pressure recorded by this method do not reveal the points of opening and closure of the carotid-jugular path.

visible changes in the femoral arterial pulse. The arterial pressure from such an experiment is recorded in Figure 3. Although the femoral artery was fuller and the walls were more taut when the arteriovenous opening was closed, the pressure tracings fail to show when the opening was closed or open. The pressure changes were not sufficient to surmount those that occurred with respiration.

This experiment (with the one previously described, in which both carotids and jugulars were united) shows clearly that when arteriovenous communications are established between vessels with normal walls, the results are different from those that occur in arteriovenous fistula following trauma. In normal vessel walls the vasomotor defense

against hemorrhage is operative, whereas in diseased walls the leak is constant and unaffected by vascular constriction. Two arteriovenous communications, each found at necropsy to have a circumference of 7 mm., would in a 12 kilogram dog provide a proportionately much larger leak than a unilateral arteriovenous fistula in the femoral artery of man. In the experimental dog, however, we are dealing with the cut ends of normal arteries, which respond with vasomotor constriction as a defense against hemorrhage, but in wounded patients the arteriovenous fistulas are found in vascular walls that have lost their unstripped muscular fibers where the fistulas form.

CONFUSION WITH AORTIC INSUFFICIENCY

In several French publications during and since the war patients similar to our first one are described as having cardiovascular symptoms like those of insufficiency of the aortic valves. The authors describe the pulse as having a celer character quite like that of aortic insufficiency, and the heart is also described as having the size and contour seen in this valvular defect. According to our observations the size and contour of the heart and the pulse differ greatly in the two conditions. The size and contour of the heart will be reserved for later discussion, and for the present we will describe the pulse character and the arterial blood pressure.

Celerity of the pulse as described in the French publications is not celerity in arterial pressure variations but in extent of excursion of the arterial wall. As shown in our experiment in which only one carotid of a dog was connected with the jugular vein, the opening of the arteriovenous communication caused a visibly increased excursion of the exposed femoral artery, but the systolic and diastolic pressure failed to show when the arteriovenous communication was open or closed. By palpation the opening and closure of the arteriovenous communication could be accurately perceived, and still the mercury manometer was not sufficiently delicate to record the variations in pressure. In our second patient, who had arterial sclerosis, closure of the leak changed a pulsus celer into a pronounced pulsus durans, with a rise of 40 mm. of mercury in the maximum arterial pressure, but in spite of this marked visible and palpable transformation from pulsus celer to pulsus durans, the pulse pressure remained the same, as measured by the pneumatic cuff on the arm.

To obtain accurate data on the relation between pulse pressure and arteriovenous fistulas, we employed the Hurthle apparatus designed for the purpose, but our results were equivocal. The nature of the experiment was such that other factors than the A-V communication came into play, and the results gave both negatory and confirmatory

results, as one chose to measure the pulse pressure at selected intervals. The results were not as satisfactory as those obtained with the mercury manometer. So far as our endeavors are concerned, we are compelled to abide by the results of the pneumatic cuff, which gave the same results not only in our cases but in the cases of four other observers, who report the unchanging pulse pressure although the fact did not arouse their interest.

Whether the cuff is an absolutely correct method or not for measuring pulse pressure does not affect the value of the clinical observations. The fact remains that, with the best clinical method for the purpose, pulse pressure is found to be unchanged with alterations in maximum pressure in this lesion only. Furthermore, when closure of an A-V opening does not modify the systolic pressure, the lesion is of no serious significance for the circulation.

Figure 4 was made by a mercury manometer connected with the carotid artery of a dog in which the proximal ends of the cut abdominal aorta and cava were connected by a paraffined U-tube. At the points marked *S*, the A-V communication was shut, and at *O* it was opened. The tracing shows the systolic pressure much higher and the pulse pressure smaller during the shut periods. There is a difference of 25 mm of mercury in pressure between the two periods, but the pulse pressures differ only by 4 mm. Furthermore, during the closed periods the pulse pressure recorded is the smaller, which differs from what happens when arterial pressure is raised by other means. Even by this recording method, as the pressure rises from the use of epinephrin the pulse pressure increases.

Although the mercury manometer does not accurately trace the pulse pressure, it betrays gross changes. This is shown in a carotid pressure tracing in an experiment of the same kind. At *S*, Figure 5, the A-V communication was closed, and at *O* it was open, then at *ad* the drum was stopped and 5 minimis (0.3 cc) of 1:1,000 epinephrin were injected intravenously. With the A-V communication left open, the pressure rose from 90 to 130 mm. These pulse pressure changes are the reverse of those which occur when an A-V communication is opened and closed, as shown by the mercury manometer. Epinephrin raises the blood pressure and enlarges the pulse pressure, closing an A-V opening raises the arterial, but does not increase the pulse pressure. While the pulse pressure was enormously increased under the maximum effect of epinephrin, at *S'* the A-V opening was closed and at *O'* again opened. Of course here we have two operating factors, one a constant, that is, the opening and closure of the A-V communication—and the other a variant, that is, vasomotor pressor effect. But in the periods of *S'* and *O'*, where the pressor effect seems probably

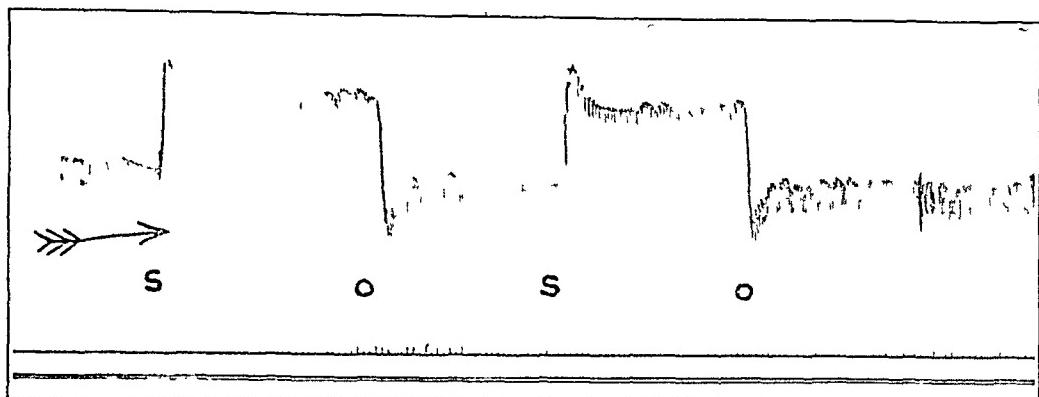


Fig 4.—The tracing was made by a mercury U manometer connected with a carotid artery in a dog with the central ends of the cut aorta and cava connected by means of a paraffined U-tube At *S* the aorta was closed At *O* the aorta was released

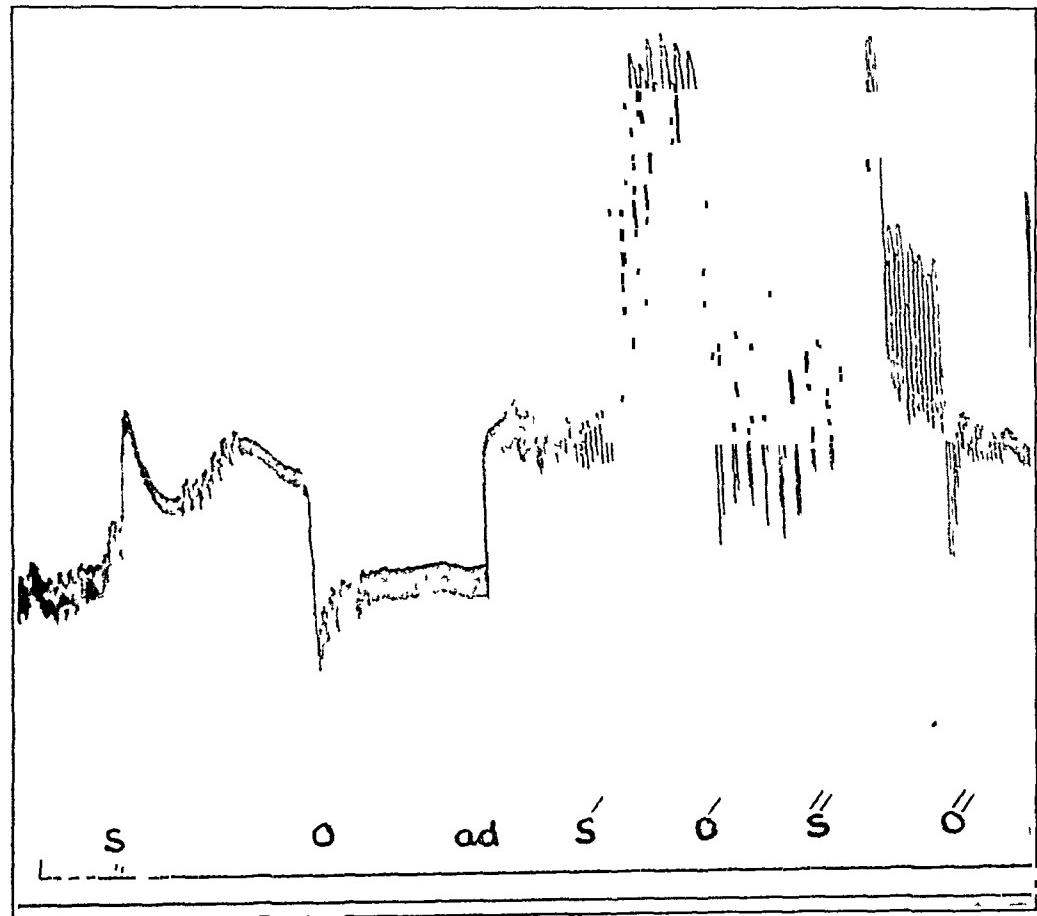


Fig 5.—At *S* the communication between the aorta and cava was closed At *O* it was opened At *ad* the drum was stopped and epinephrin injected, followed by the prompt rise in pressure At *S'* the arteriovenous opening was closed, at *O'* it was opened, at *S'''* it was closed, and at *O''* it was opened

the same, the pulse pressure is little changed at O' by opening the A-V passage, although the systolic pressure is much lowered by the procedure. Insufficiency of the aortic valves lowers the diastolic pressure and is attended with a compensatory rise in the systolic pressure. Every change in maximum blood pressure that occurs with any disease of the aortic valves or the aorta or peripheral arteries is attended with change in the pulse pressure.

The rise in maximum blood pressure of our second patient when the A-V communication was closed came promptly with the closure. When the femoral artery above the fistula was compressed at the end of a cardiac systole, the next arterial pulse apparently had the maximum rise, and this blood pressure and pulse pressure were maintained until the A-V communication was reopened, when the return to the former arterial and pulse pressure as promptly followed. This change is too prompt to include any vasomotor factor.

The mechanism of an arteriovenous leak differs from that of the central leak (aortic insufficiency) and of the peripheral leak (vasomotor relaxation). In the central leak the mechanism is operative during diastole and not in systole, in the arteriovenous leak and in the vaso-motor relaxation the mechanism is operative during the entire cardiac cycle, but in the latter there is modification of the vascular capacity.

LESIONS SIMULATING ARTERIOVENOUS FISTULA

This absence of change in pulse pressure is not only pathognomonic of the lesion, but it also serves to differentiate between arteriovenous fistula and conditions that may simulate it. The following case illustrates this point.

CASE 3.—A healthy young man was wounded by a shot from an automatic pistol. The ball passed through the lower end of Hunter's canal. Over this area there was a painful swelling about 7 cm long and 4 cm wide. The region was sensitive to pressure, and over the swollen area there was a loud murmur during the entire cardiac cycle with accentuation during the systole. Over the same area there was a strongly palpable thrill, which was first perceived three days after the accident. There was no venous distention. When the femoral artery on the affected side was compressed, the blood pressure as measured in the arm remained systolic, 110, diastolic, 70, but the cardiac rate was reduced from 72 to 56.

Was this an arteriovenous aneurysm? It was not. In the first place, the prompt appearance of the palpable thrill after the accident proved that there would be no arteriovenous fistula. As seen in all our cases, about two weeks are required after the occurrence of a wound before a fistula forms. In the second place, the blood pressure was not changed by compression of the femoral artery. There was, it is true, marked slowing of the pulse, which has been repeatedly stated in medical literature to be a sign of arteriovenous fistula, but the slowing

of the heart rate seems to be caused by some afferent nerve impulse that is released when the wounded artery is compressed, and cannot be linked with any effect on the hydraulics of blood flow.

At operation there proved to be no arteriovenous communication in this case. The artery and vein were completely severed, and all four ends of the two vessels lay free within a blood sac. The free ends of the vein evidently acted as clapper valves and thus prevented blood from entering either the proximal or distal end. The free distal end of the artery, however, had so much resistance in its wall that the lumen remained partly open and thus admitted sufficient affluent blood so that the pulses in the dorsalis pedis and posterior tibial of the affected side were plainly palpable.

SIZE OF THE HEART

The size and contour of the heart are important, and a clear exposition of both may lead to a correct diagnosis when the arteriovenous fistula cannot be eliminated by arterial compression on account of pain or inaccessibility. In our first case, the fistula was accessible, but it could not be eliminated on account of extreme tenderness to pressure in Scarpia's triangle. The patient's heart was enlarged, as shown by the palpable impulse and dulness to the left of the midclavicular line. The area and force of the cardiac contact with the anterior thoracic wall were much increased, as shown by the broad quadrilateral impulse that was plainly palpable over the entire anterior area of the right ventricle. In spite of the enlarged heart, high venous pressure and great hepatic pulse, we were skeptical that myocardial incompetence was a causative factor, because there were no evidences of stasis in the pulmonary vessels, and the precordial area of dulness did not extend to the right of the sternum, nor was there any evidence of flattening of the subcardial diaphragm to the right of the median line. Because there was much enlargement of the ventricles and no evidence of pulmonary stasis or enlargement of the right auricle, we advised operation. Immediately after the operation the broad area of cardiac impulse over the right ventricle ceased. The contact of the right ventricle with the chest wall was much less vigorous, but the precordial area of dulness was unchanged until two weeks after the operation, when the heart returned to its normal size.

The following case well illustrates the need of interpreting the size and contour of the heart when the arteriovenous fistula is beyond digital control.

CASE 4.—The patient was seen by one of us (C. F. H.) a month before the first patient described in this paper came under observation. (It was not until the second experience that the former case could be satisfactorily interpreted.) A young man, aged 25, two months before was struck with great violence just above the right sternoclavicular joint by the handle of a mop. There was no

wound of the skin and no immediate results to indicate that there had been a serious injury. Two weeks later the patient suddenly developed a sense of extreme fulness and oppression over the upper thorax, which was caused by the establishment of a communication between the carotid artery and the jugular vein close to the innominate vessels. The jugular vein and bulbus venosus were greatly distended and pulsated violently and synchronously with the arterial pulse. The liver was four fingerbreadths below the costal margin in the nipple line and showed a strong systolic pulsation. The impulse of the left and right ventricles was greatly increased in intensity, and the area of the heart extended to the left midway between the nipple and anterior axillary lines. The area of heart dulness did not extend to the right of the sternum in the third, fourth and fifth interspaces, but there was an area of dulness like a band about 2 cm wide to the right of the manubrium from the first to the third ribs.

With this combination of cardiac enlargement, venous engorgement and hepatic pulsation there was no evidence of pulmonary rigidity or edema, and there was no evidence of flattening of the subcardial diaphragm to the right of the median line. The entire right costal margin moved laterad in inspiration.

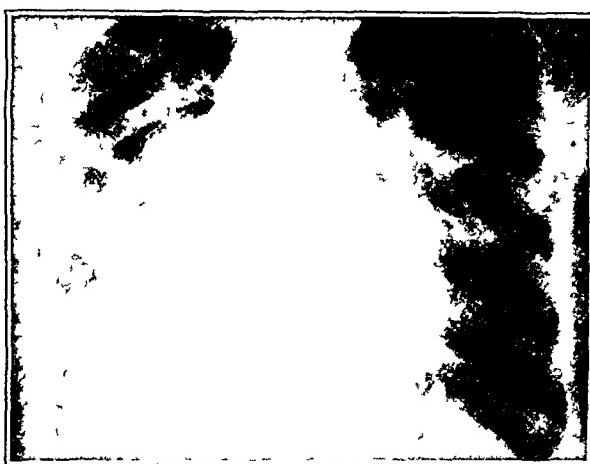


Fig 6.—Note the large globular erect heart without any evidences of flattening of the subcardial diaphragm to the right of the median line

The inner part of the left costal margin was slightly diminished in its laterad movement, but the outer half moved readily outward in inspiration. During systole and diastole a loud murmur was audible, which had its maximum intensity at the right border of the manubrium. The pulse had a celer character of moderate excursion. Figure 6 was taken at the time, and shows the moderate globular enlargement of the heart.

A few weeks later surgical relief was attempted, but the patient succumbed during the operation.

Although this patient exhibited marked signs of venous and hepatic stasis he was able to walk about, and although he could exercise little he did not suffer from air hunger when at rest. These facts, together with the absence of pulmonary edema and the absence of ectasis of the right auricle, justified the diagnosis of arteriovenous fistula. The location and contour of the right heart border and the inferior contour of the heart as revealed by the movements of the costal borders, are

the essentials in making a diagnosis in such cases as this. One may be greatly misled if the presence of cardiac enlargement, pulsus celer and the murmurs are accepted as proof of venous stasis from cardiac incompetence.

CARDIAC ENLARGEMENT

The behavior of the heart in arteriovenous fistula is amazing. The large and vigorous impulse that takes in the entire precordial aspect of both ventricles may lead one to overestimate the size of the heart and erroneously make a diagnosis of cardiectasis. When the A-V opening is closed, the impulse over the area of the right ventricle ceases immediately and only the apical impulse of the left ventricle is perceptible. This change occurs directly after the closing of the arteriovenous fistula, but in severe cases, like the first one described, the percussion borders will not return to the normal limits until after two weeks. In our second case, which was complicated with arteriosclerosis, this change in the character of the precordial impulse could be produced at will by alternately compressing and releasing the femoral artery above the site of the fistula. When the A-V communication is open, the diastolic-systolic excursion of the heart is increased and the heart assumes a globular contour, although the area of precordial projection may be little changed. The deception is quite like that experienced in estimating the size of the heart in acute exophthalmic goiter. The examiner is likely to overestimate the size of the heart in this disease, because the systolic excursion is increased to accommodate an increased minute volume flow of blood. The impulse becomes accessible over the entire precordial area, and the heart is therefore assumed to be much enlarged. Only accurate percussion of the borders of the heart and study of the costal margin movements save one from this error. In acute exophthalmic goiter the costal margin movements never indicate any flattening of the subcardial diaphragm. In chronic exophthalmic goiter that presents evidences of myocardial decompensation and renal disease, the subcardial diaphragm will be flattened as occurs in cardiectasis from other causes.

In producing these cardiac changes experimentally we had no success in survival experiments because in such experiments we could not obtain any great changes in blood pressure—the A-V leak was insufficient. However, when the proximal ends of the abdominal aorta and cava were united by a U-tube and the thorax and pericardium opened, we had a satisfactory view of the two ventricles and the right auricle, and the changes in the size and excursion of these parts were plainly in view as the A-V communication was alternately closed and opened by compressing and releasing the abdominal aorta. Under the fluoroscope the heart was seen to swell into a globular contour but was little enlarged. Roentgenograms were then taken with the tube 6 feet

(182.8 cm) away. Figure 7, A and B, shows the difference in the contour of the heart when the A-V flow was closed and free. Later the thorax was freely opened, artificial respiration begun and the pericardial sac opened and used as a support on which the heart rested. On opening and closing the A-V path, the heart was seen to respond in a manner that suggested the changes in excursion and celerity of the arterial wall from the same cause. The ventricles visibly swelled and greatly increased their excursion as the communication was opened, but the right auricle increased little in size and showed a comparatively slight increase of diastolic-systolic excursion. The increase in volume and excursion of the ventricles was plainly a compensatory effect to meet the need of the increased cardiac output that resulted from the arterial

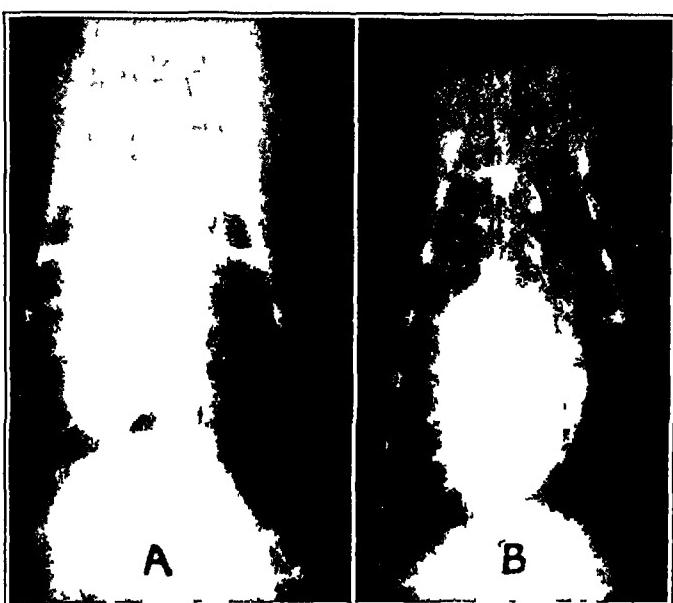


Fig 7.—The aorta and cava of the dog were connected by a U tube. A is a 6 foot roentgenogram with the arteriovenous communication closed. B is a 6 foot roentgenogram with the arteriovenous communication opened. Note the change in contour with slight increase in the transverse diameter of the heart.

leak. Ten cc of 1:1,000 epinephrin were then injected into the jugular vein at intervals of ten minutes. The first few injections caused the heart to increase in size, and the aorta became greatly distended and elongated, so that it resembled the elongated and dilated sclerosed aorta in patients with a high degree of peripheral arterial resistance. After several repetitions of the epinephrin injections, the heart dilated from incompetence and went into fibrillation of auricle and ventricle. As decompensation occurred, attended by great ectasis of the right ventricle and auricle, one perceived the striking contrast between ectasis of the heart chambers and compensatory dilatation in response to an

increase of minute volume flow. Why the subcardial diaphragm is flattened in ectasis and not in compensatory dilatation was apparent. In cardiectasis there was great enlargement and downward extension of the right auricle and base of the right ventricle, whereas in compensatory dilatation there was an increase in the circumference of the mesocardium but no depression of the ventricular base or of the auricle as the circumference of the ventricle enlarged.

Cardiac enlargement compensatory for an increased volume flow produces a globular enlargement restricted to the mesocardium. There is slight if any dislocation of the apex, and the circumference at the base of the heart and at the atrioventricular sulcus is not increased. The heart remains in an erect position and does not encroach on the diaphragm. In arteriovenous fistula, chlorosis and acute exophthalmic goiter, the heart takes on this globular contour and increase of its middle circumference in response to the enlarged minute volume flow of blood. The diastolic-systolic excursion of the ventricles is enlarged. The force and area of precordial excursion of the ventricles are greatly increased and give the impression of great cardiac dilatation, when in reality percussion, movement of the costal borders, and the roentgen ray all indicate only a moderate globular enlargement of the ventricles. In acute exophthalmic goiter, a degree of volume increase that would suffice in myocardial disease to depress the subcardial diaphragm will not show any modification of inspiratory movements of either costal border. The reason for this is quite apparent if the changes are observed in heart volume and contour when epinephrin in large amounts is given to a dog with a large A-V fistula. When the fistula is open, the heart increases in its midcircumference and diastolic-systolic excursion without encroaching downward but as acute dilatation and fibrillation follow the large dosage of epinephrin, the circumference of the ventricles at the atrioventricular sulcus greatly enlarges, the right auricle protudes with a large semilunar contour to the right of the base of the ventricle, and the heart encroaches on the diaphragm. These observations provided us with a satisfactory explanation for the discrepancy between the costal border movements in exophthalmic goiter and in cardiac disease, when apparently both conditions should produce corresponding effects on the costal border movements.

From our clinical observations and animal experiments we were convinced of the ventricular enlargement that immediately attends short-circuiting of the circulation through an A-V opening. When the teleoroentgenograms were made, however, they were disappointing. They did not show as much enlargement in the transverse direction as we expected to see. The cardiac enlargement as perceived by clinical examination and by direct inspection in animal experiments indicated

the primary enlargement to be chiefly in an anteroposterior diameter in the early stages of the disease, and enlargement of the transverse diameter to be a later development

To present graphic evidence of ventricular enlargement as a promptly developing sign of A-V fistula, the size of the heart was recorded by a plethysmograph. The abdominal aorta and cava were united by a U-tube, the thorax opened and artificial respiration employed. The ventricles only were included in the plethysmograph. The upper tracing in Figure 8 shows the blood pressure taken by a mercury manometer from the carotid artery. The lower tracing is that of the plethysmograph. C marks the closure and O the opening of the A-V communication. The excursions of the plethysmograph were graduated immediately after the experiment by introducing measured quantities of water

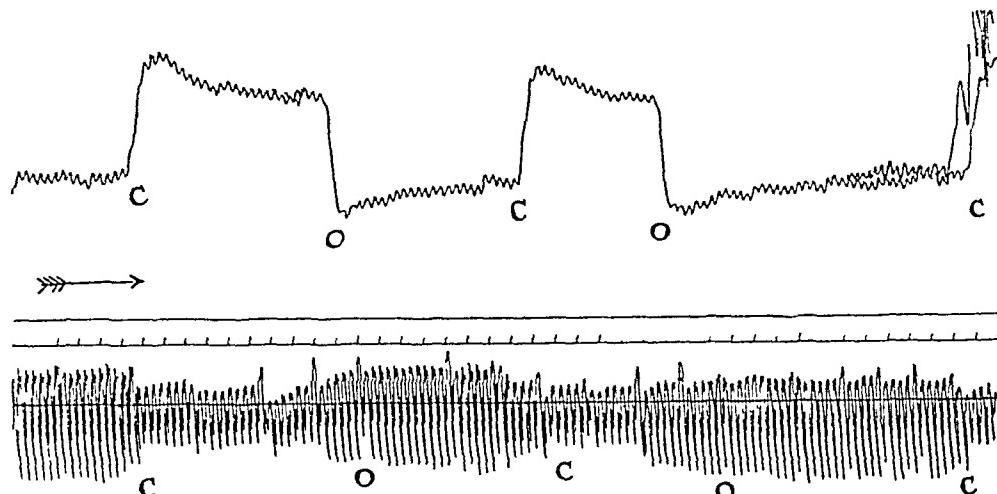


Fig 8.—The upper line is a mercury manometer tracing from the carotid artery. The lower line is from the plethysmogram of the heart. The time recorded is in seconds. At C the arteriovenous communication was closed, and at O it was opened

into the system. When the results of the graduation were applied to the tracings, it was found that the excursion of this heart amounted to 6 cc when the A-V opening was closed, and 11 cc when opened. This measurement is in all probability exaggerated by the swing of the registering lever, but it is not surprising after the change in excursion has been observed in an animal experiment. The time marker is in seconds.

Figure 9 is a tracing taken on a fast drum to show the working of the plethysmograph. The up stroke traces diastole and the down stroke systole.

These observations show how a heart may be enlarged anteroposteriorly and fail to show by percussion or roentgen ray any transverse enlargement. This is true of well compensated cases of initial

stenosis when only the right ventricle is enlarged, and it is also true in exophthalmic goiter when both ventricles are enlarged and the auricles are not. The only physical sign that betrays the enlargement is the enlargement of the area of precordial impulse due to the right ventricle partaking of this activity as well as the apex of the left ventricle. When a clinician establishes the evidences for anteroposterior cardiac enlargement, he should not recede from his position because the roentgen may fail to reveal an enlargement of the precordial area.

THE HEPATIC PULSE

The physical sign of striking importance that remains for discussion is the hepatic pulse. It will be remembered that in three of the reported cases—the two in which the A-V fistula formed in the femoral vessels after gunshot wounds, and the one in which the fistula formed between the carotid and jugular after a sharp blow from the long wooden

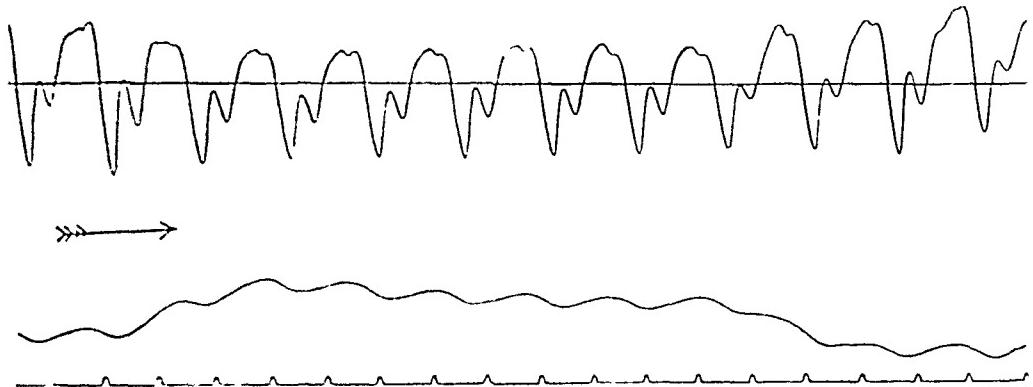


Fig. 9.—This plethysmographic tracing is from the same experiment in which the tracing in Figure 8 was made, and merely shows the correct working of the plethysmograph. The time recorded is in one-fifth seconds.

handle of a mop—there were systolic pulsations in the liver. In the case of the woman with the gunshot wound, as the artery above the fistula was compressed the hepatic pulse disappeared with the cardiac systole that followed the arterial compression, so that there can be no doubt that the systole of the right ventricle played no part in producing the hepatic pulse. It depended on two factors—an adequate distention of the cava, and a direct pulse wave from the artery into the tributaries of the cava. In our experimental animals there was no hepatic pulse palpable or visible when the abdomen was opened and the liver brought plainly into view, and in none of them were we able to procure sufficient pressure in the cava to obtain an hepatic pulse. It might have been expected that when the lumen of the aorta was connected with the cava there would be a considerable rise in the cava pressure, but that was not the case. Our experiment was of such short duration that the increased output of the heart was adequate to care for this contingency.

In the clinical cases the problem of hydraulics of blood flow must have been nearly, although not quite, identical with that in our experimental animal, the essential factor being the cardiac inability to compensate over a prolonged period for the enlarged minute volume flow necessitated by the arteriovenous communication.

The hepatic pulsation in our patients was not an index or measure of cardiac decompensation. It came directly from the arteriovenous opening, but should the arteriovenous leak be ever so large that alone will not suffice to produce an hepatic pulse. The pulsation of the liver is not obtained until the factor of large elevation in venous pressure is added. The arteriovenous leak does not suffice to produce the liver pulse until the cava pressure increases as a result of the incompetence of the heart to supply the increased output demanded as a result of the arteriovenous fistula. Under such conditions, closure of an arteriovenous communication produces an amazing cure. By this procedure the venous system as well as the myocardium profits directly. The work of the heart is greatly lessened, and both the direct and the indirect source for venous stasis is corrected. Our patient who was operated on and promptly restored to health after so long and exhausting an illness submitted to an examination two years after the operation. He was then in perfect health and seemingly was concerned only about his pension, which had been granted on the basis of total disability.

VENTRICULAR ECTOPIC TACHYCARDIA COMPLICATING DIGITALIS THERAPY*

WILLIAM D REID, M.D.

BOSTON

Paroxysmal tachycardia originating from an ectopic focus in the ventricle is a relatively rare type of cardiac arrhythmia. Robinson and Hermann,¹ in 1921, found reports of only sixteen cases, not all of which they accepted as proved, and to which they added four additional cases.

This type of paroxysmal tachycardia can be differentiated from that of auricular origin only by the help of the electrocardiograph. Even then, unless the electrocardiogram contains the beginning or the ending of the paroxysm, it is not always possible to determine the exact origin of the rhythm, since it is known that in some instances of paroxysmal auricular tachycardia the ventricular complexes may be aberrant, due to imperfect conduction in the ventricular conduction paths during the rapid rate.²

When the tracing does not contain the first beat of the paroxysm, search should be made for evidence of the P wave, and if it can be shown that the auricles are beating at a different rate from that of the ventricles, the paroxysm is almost surely ventricular in origin. Electrocardiograms taken shortly before or after the paroxysm of tachycardia should be examined, if they contain isolated ventricular extrasystoles which are an exact replica of the complex which is regularly repeated during the paroxysm, it is the more probable that the latter is of ectopic ventricular origin.

Lewis³ pointed out the relation of ventricular ectopic tachycardia to thrombosis in the coronary artery. Robinson and Hermann,¹ in the paper already mentioned, also emphasized the frequent association of this arrhythmia with coronary occlusion and infarction of the myocardium.

Later Lewis and Levy⁴ observed ventricular ectopic tachycardia in cats under the influence of chloroform and epinephrin.

* From the Heart Laboratory of the Boston City Hospital

1. Robinson and Hermann. Paroxysmal Tachycardia of Ventricular Origin, and Its Relation to Coronary Occlusion, *Heart* 8 59 (Feb.) 1921

2. Lewis, T. Mechanism and Graphic Registration of the Heart Beat, New York, Paul B Hoeber, 1920, p 262

3. Lewis, T. The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, *Heart* 1 98, 1909-1910

4. Lewis and Levy. Heart Irregularities, Resulting from the Inhalation of Low Percentages of Chloroform Vapour and their Relation to Ventricular Fibrillation, *Heart* 3 99, 1911-1912

In his study of the action of strophanthin on the cat's heart, S A Levine⁵ noted this same arrhythmia. In one experiment it did not appear until 90 per cent of the minimum lethal dose had been injected, and without the previous appearance of extrasystoles.

The administration of quinidin sulphate has been followed by the appearance of ventricular ectopic tachycardia, and dogs have occasionally died with this arrhythmia.⁶ R L Levy⁷ reports three cases in man. Fortunately they were of short duration, lasting always less than twenty hours, and sometimes disappearing in the course of three hours after the last dose of quinidin was given. Another case was reported by W J Kerr and W L Bender,⁸ certainly some of the curves appear to be axamples of ventricular ectopic tachycardia.

Eggleston and Wyckoff⁹ noted runs of this form of ventricular tachycardia in one case in their study of the absorption of digitalis in man, a good recovery followed. C Schwensen,¹⁰ of Copenhagen, has reported a fatal case of ventricular ectopic tachycardia as a complication of the administration of digitalis. The electrocardiograms of the other case, described in Schwensen's paper, showed ventricular extrasystoles of multiple origin but not a true paroxysm of tachycardia of ventricular origin.

Wolferth and McMillan¹¹ have recently reported four more cases of ventricular ectopic tachycardia. They are disinclined to credit the action of digitalis as a cause, in their cases digitalis was used in only one of the four, and the weight of evidence was against the paroxysm of tachycardia being drug induced. These same observers point out that the combination of auricular flutter or fibrillation with paroxysmal tachycardia is extremely rare (except when the latter is caused by drugs), until their report only one case of each having been recorded, both by Gallavardin¹².

5 Levine, S A. The Action of Strophanthin on the living Cat's Heart, J Exper Med 29 485 (May 1) 1919

6 Cohn, A E, and Levy, R L. Experimental Studies of the Pharmacology of Quinidine, Proc Soc Exper Biol & Med 18 283, 1921

7 Levy, R L. Clinical Studies of Quinidine, Arch Int Med 30 451 (Oct) 1922

8 Kerr, W J, and Bender, W L. Paroxysmal Ventricular Fibrillation with Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart-Block while Under Quinidin Sulphate Therapy, Heart 9 269 (Dec) 1922

9 Eggleston and Wyckoff. The Absorption of Digitalis in Man, Arch Int Med 30 133 (Aug) 1922

10 Schwensen, C. Ventricular Tachycardia as the Result of the Administration of Digitalis, Heart 9 199 (April) 1922

11 Wolferth and McMillan. Paroxysmal Ventricular Tachycardia Report of One Case with Normal Type of Auricular Mechanism and Three with Auricular Fibrillation Arch Int Med 31 184 (Feb 15) 1923

12 Gallavardin. Tachycardia Paroxystique Ventriculaire, Arch d mal du coeur 13 121 (March) 1920. Tachycardia Ventriculaire Terminale, Arch d mal du coeur 13 207 (May) 1920

CASE REPORTS

CASE 1—History—A housewife, aged 50, entered the Boston City Hospital, Sept 24, 1922. She complained of dyspnea, precordial pain, palpitation, a slight cough, swelling of the ankles and general weakness. One year ago she first noted dyspnea on slight exertion, this was accompanied by a mild nonproductive cough. The symptoms had gradually increased and during the two months before she entered the hospital there had been palpitation, precordial pain and edema of the ankles. Measles was the only disease recalled. She said she had not had rheumatic fever, chorea, tonsillitis, pneumonia, typhoid fever, puerperal sepsis, any acute fever or venereal disease. She weighed 200 pounds (90.7 kg.), her weight had been unchanged for years.

Physical Examination—The patient was markedly cyanotic and orthopneic, and her expression was distressed. Visible throbbing of the carotid arteries was noted. The lungs were normal to percussion and auscultation except for a

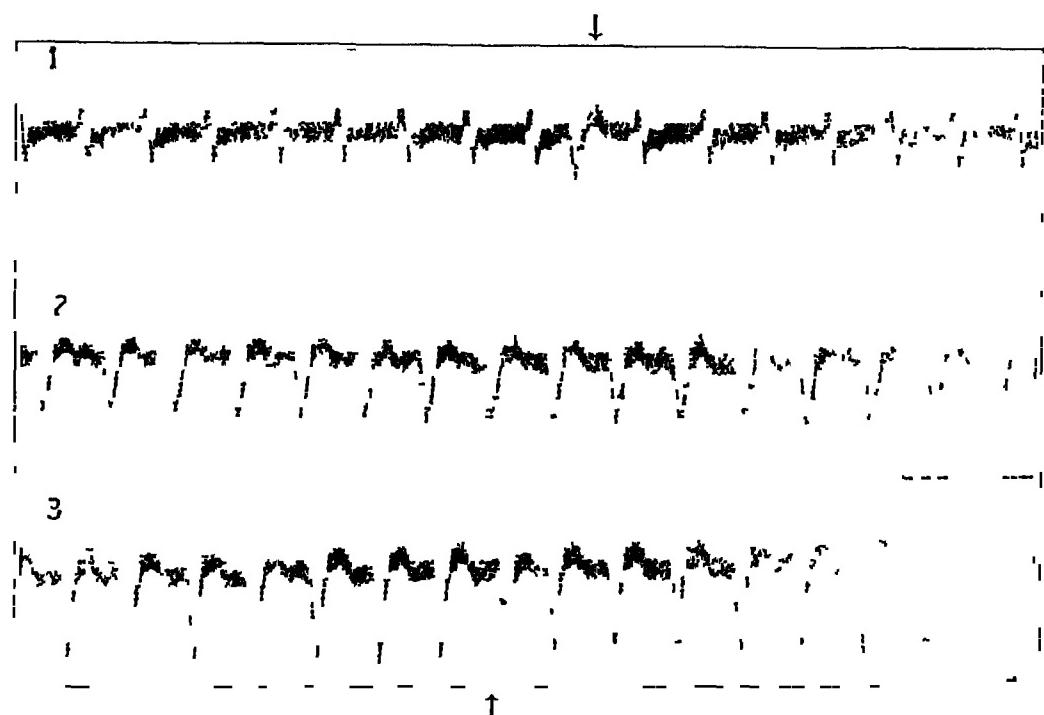


Fig 1 (Case 1).—At the points marked there is an apparent interruption of the paroxysm. Careful scrutiny of the tracing discloses an irregular activity of the auricles. In this and the subsequent electrocardiograms the coarse abscissas mark off periods of 0.2 of a second, the finer ordinates have a value of 0.1 millivolt.

few râles at the bases. The heart impulse was palpable in the fifth interspace outside the midclavicular line, by percussion the cardiac borders were found to be 4 cm to the right and 14 cm to the left of the midsternal line. There was a systolic murmur at the apex, well transmitted to the base and to the left axilla. A soft diastolic murmur was noted at the aortic area and well transmitted along the left sternal margin. The rhythm was absolutely irregular, the apex rate was from 130 to 140, the radial 98 to 110. The abdomen was distended. There were shifting dulness and fluid wave. The liver was not felt. There was considerable soft edema of the lower legs. The blood pressure was systolic 160 to 170, diastolic 110 to 120. The Wassermann reaction was negative.

Course of Illness—September 27. The patient was much relieved, the edema was almost gone. The heart rate was about 90, the rhythm irregular,

the pulse deficit almost gone. The rhythm was apparently that of auricular fibrillation with some ventricular extrasystoles. The patient was nauseated early in the morning.

September, 29. The patient was very restless sleeping only in naps, and trying to get out of bed frequently during the night. She vomited in the morning, had a cold perspiration and talked at random. The heart action was observed to become rapid suddenly and regular. This was displaced after about two minutes by the former irregular rhythm at the rate of about 90 per minute. These two rhythms alternated at intervals of one to three minutes for about three quarters of an hour and then the regular tachycardia of a rate of about 150 per minute became permanent. An electrocardiogram confirmed the clinical diagnosis of ventricular ectopic tachycardia.

September 31. The ventricular tachycardia had persisted and the patient had lost ground gradually with signs of progressive heart failure of the congestive type. Death occurred two days and three hours after the onset of the tachycardia.

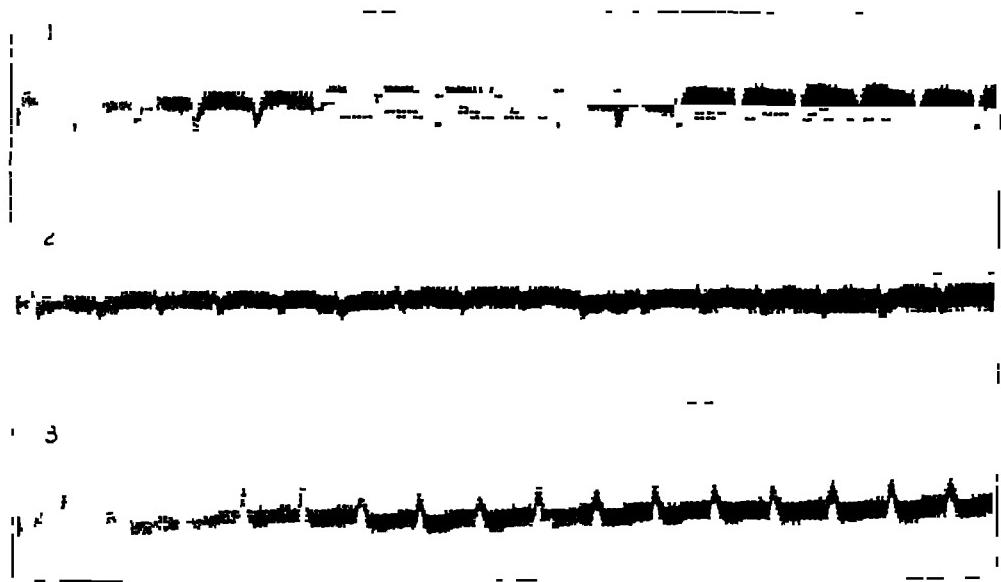


Fig 2 (Case 2)—Ventricular ectopic tachycardia, rate 140

CASE 2.—A man, aged 63, entered the Boston City Hospital on Dec 23, 1922. He complained of periodic shortness of breath. During the past two years he had had attacks of shortness of breath lasting about one hour each. Twenty-four hours before entering the hospital a similar attack began. He was raising gas from the stomach, freely. There was also a dry cough and moderate precordial pain with the present attack. He had had excellent health until the present illness.

Physical Examination.—This revealed considerable cyanosis, respiration rapid, labored and accompanied by audible tracheal râles. The lungs showed dulness at the bases with moist râles throughout. There was percussion dulness of the heart measuring 4.5—16.5 cm. The rhythm was absolutely irregular, the rate rapid and a large pulse deficit was noted. There was marked tenderness of the liver. Soft edema was present from the feet to the thighs and over the lower part of the back.

Course of Illness.—December 24. The heart sounds were almost regular, interrupted by occasional extrasystoles. The patient appeared to be much relieved.

December 28 In the forenoon a regular tachycardia, rate 140, appeared suddenly This persisted until late in the afternoon, when there were periods during which the heart rate was 58 per minute and regular except for occasional coupling During the tachycardia there was moderate dyspnea and precordial pain Death occurred suddenly during the night

Necropsy—The pericardium contained 30 cc of clear fluid The heart weighed 320 gm On the surface were numerous small "milk patches" The coronary arteries showed on the surface as opaque, white wavy lines The myocardium was reddish brown, the consistency was firm The right auricle was somewhat dilated The cusps of the aortic valve were thickened and yellow in places, and one old fibrous vegetation persisted The mitral valve was somewhat thickened The measurements were tricusped valve, 14 cm, pulmonary valve, 8.3 cm, mitral valve, 10.5 cm, aortic valve, 7.3 cm, the left ventricle was 13—2 cm, the right ventricle 0.5 cm The coronary arteries showed patches of sclerosis There was a moderate amount of sclerosis, in the aorta, most marked in the lumbar region

Anatomic Diagnosis—The diagnosis was hypertrophy and dilatation of the heart, moderate arteriosclerosis of the aorta and coronaries

CASE 3—A woman, aged 80 years, entered the Boston City Hospital on Feb 5, 1923 During the preceding months the patient had been dyspneic



Fig 3 (Case 3)—Lead II, ventricular ectopic tachycardia, rate 170 Note transition to an alternating mechanism in the latter half of the tracing Lead III ventricular fibrillation About 25 to 30 seconds time elapsed between the two tracings

on slight exertion There had been frequent attacks of palpitation during the two preceding months She had done much manual labor until six weeks before, when her ankles became swollen and the dyspnea and palpitation increased She had been confined to bed for four weeks before entering the hospital and had grown worse The swelling now extended to the legs and the abdominal wall She had had measles, mumps and whooping cough when a child and one or two attacks of tonsillitis each winter during childhood There was no history of rheumatic fever, chorea, scarlet fever, etc Her maximum weight before the onset of the swelling was 135 pounds (62.2 kg)

Physical Examination—The patient was well developed and well nourished She had marked dyspnea and considerable cyanosis The cervical veins were engorged and pulsating markedly The bases of both lungs were dull, there was flatness and diminished tactile fremitus at the right base below the mid-scapular region and extending to the right lower front There was bronchial breathing and egophony above this area, with a few scattered râles There were many moist bubbling râles in the left side of the chest The heart impulse was palpable in the fifth space at the anterior axillary line, accompanied by a

systolic thrill. There was absolute arrhythmia. The apex rate was 124, the wrist rate 78, the deficit 46. There was a loud first sound at the apex with systolic and mid-diastolic murmurs. The pulmonic second sound was louder than the aortic second sound, but not accentuated. The abdomen was slightly distended, the wall edematous, no shifting dulness was detected. The edge of the liver was 2 cm below the costal margin in the right mamillary line.

Thick, brawny edema was present in the legs and dependent parts of the trunk. The blood Wassermann reaction was negative.

Course of Illness.—February 6. The heart action suddenly changed to a regular tachycardia—rate 160.

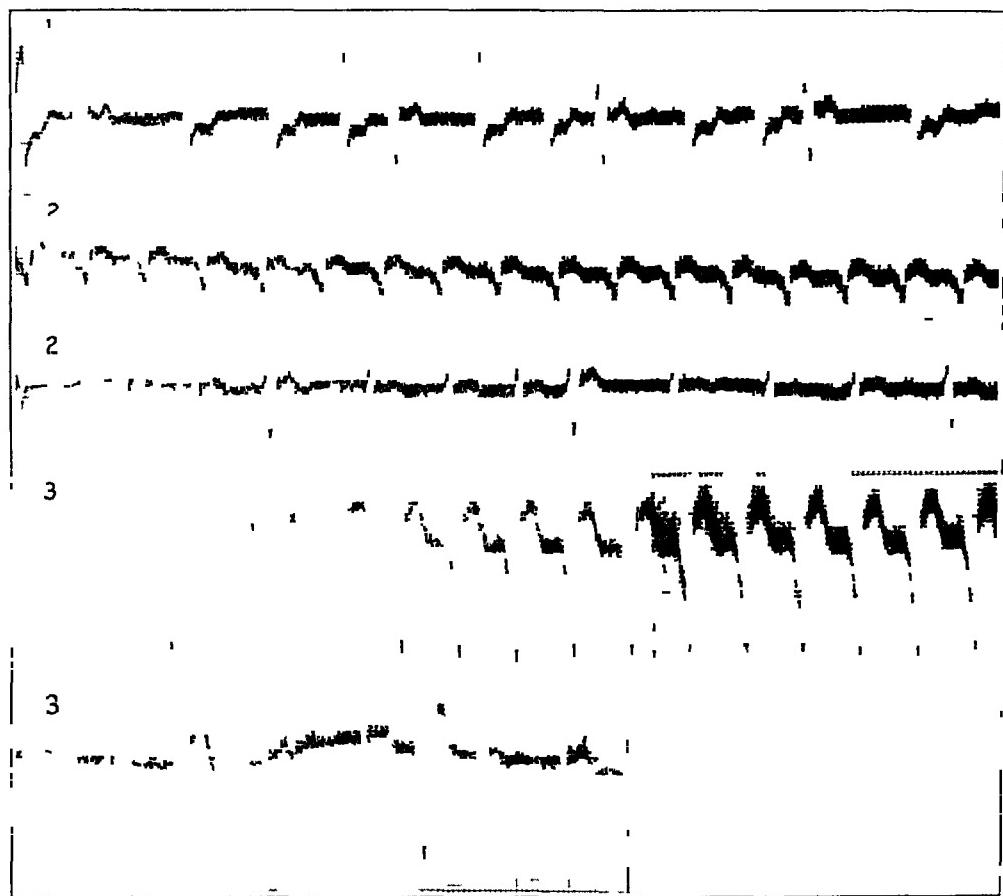


Fig. 4 (Case 4).—Ventricular ectopic tachycardia in tracings 2 and 4 (counting from above downward), auricular fibrillation with ventricular extrasystoles replicas of the ventricular complexes in the tracing just above. An interval of but a few seconds elapsed between the individual tracings.

February 7. The regular tachycardia continued but was interrupted by periods of a few seconds during which the heart rate was much slower, estimated at about 50 to 60 per minute.

An electrocardiogram was taken. The first photograph showed ventricular ectopic tachycardia, and the remaining three ventricular fibrillation. The patient was resting comfortably just before the tracing was made, death occurred peacefully as the ventricular fibrillation was recorded. Examination of the anterior chest just previous to the taking of the electrocardiogram disclosed no râles, and no tracheal râles were audible as death ensued.

CASE 4—A man, aged 47, entered the hospital on July 7, 1921, complaining of dyspnea and palpitation. For ten months he had had a sense of constriction under the sternum after exertion. This had gradually become more marked until walking on the level caused severe precordial pain. One month before swelling of the ankles and lower legs became manifest. The patient had been dyspneic, weak and afflicted by a cough with free expectoration during the week before entering the hospital. He had not had children's diseases. His cardiorespiratory history was negative. One year before he had had an operation in this hospital for the removal of calculi from the left kidney. His wife died of heart disease. He had four children living and well and one stillborn child.

Physical Examination.—The patient was orthopneic. Many coarse râles were heard in the lungs. The heart impulse was in the fifth space, 2 cm outside the nipple line. The left border of deep cardiac dulness was 16 cm

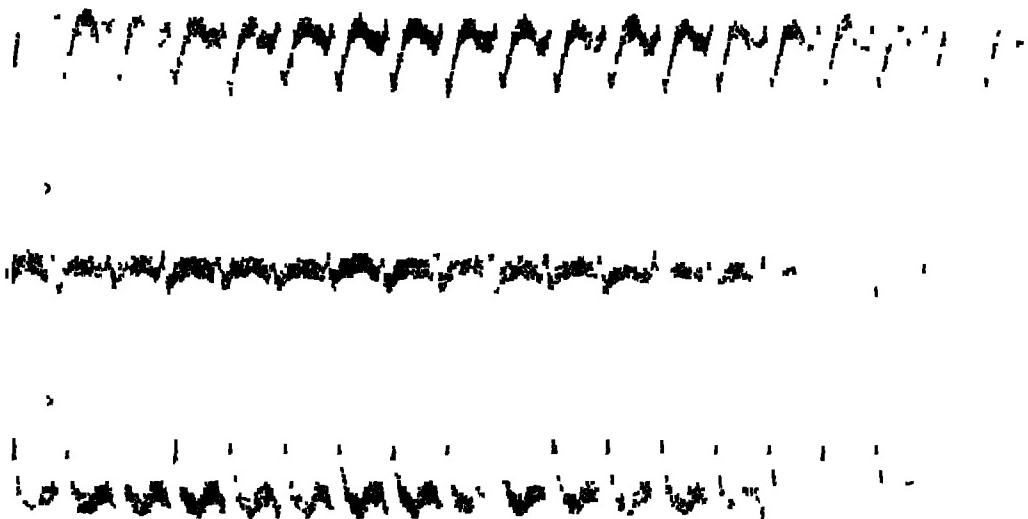


Fig 5 (Case 5)—Ventricular ectopic tachycardia, rate 174

from the midsternal line, the right border was not obtained. The rhythm was absolutely irregular, no murmurs were heard. The abdomen was distended. The liver was palpable 5 cm below the costal margin in the right axillary line; it was slightly tender. There was marked edema from the ankles to the knees. The blood Wassermann reaction was negative.

Course of Illness.—July 11. The patient had improved a little. His heart rate varied from 98 to 110. In the morning there were runs of a regular tachycardia, rate 146, lasting from one half to one and one half minutes. An electrocardiogram (Fig. 4) showed ventricular ectopic tachycardia alternating with periods of auricular fibrillation and ventricular premature beats.

July 12. The runs of the regular tachycardia had ceased.

Subsequent History.—There was no further appearance of the ventricular ectopic tachycardia. The mechanism of auricular fibrillation continued, and the patient's condition remained stationary. Death from progressive failure of the heart occurred on Sept. 12, 1921.

CASE 5.—A woman, aged 60, admitted to the hospital on Jan. 7, 1923, had known of her heart disease since 1902, but she was not confined to bed because of it.

Physical Examination—She was moderately dyspneic, not cyanosed. The heart impulse was palpable in the fifth space, just outside the midclavicular line, percussion corresponded. There was a systolic murmur with a first sound at the apex, transmitted to the base and axilla. The supraventricular dulness at the first space measured 2 by 1 cm.

Course of Illness—January 12. The patient had been slightly better. At noon the heart action changed to a fixed, regular tachycardia, rate 174 per minute. The tachycardia persisted into the night, during which it disappeared. An electrocardiogram (Fig 5) showed ventricular ectopic tachycardia.

January 13. The regular tachycardia returned for a few hours during the afternoon.

January 14. During the evening the third and last attack of regular tachycardia appeared and ceased during the night.

January 15. An electrocardiogram (Fig 6) showed normal rhythm with multiple ventricular extrasystoles. The patient died from progressive heart failure on January 20.

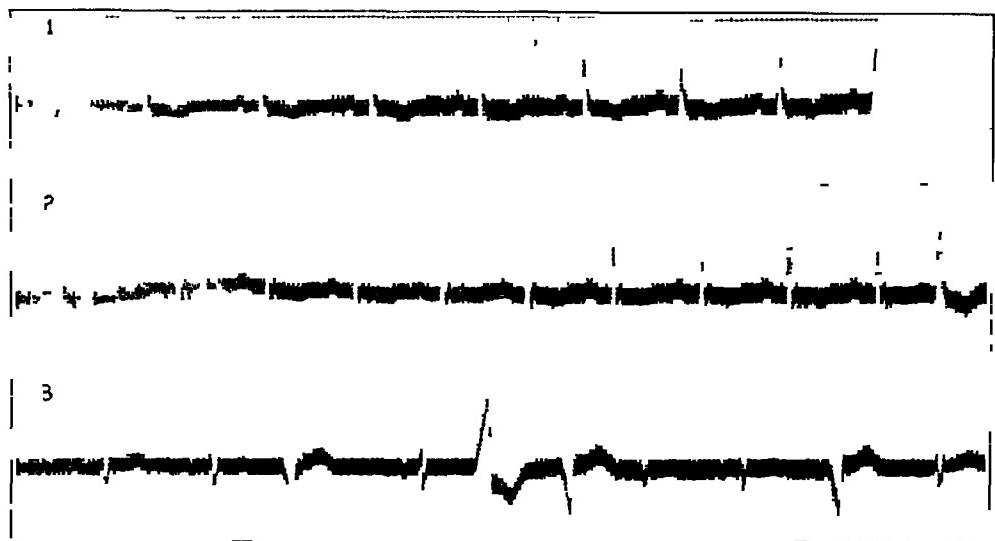


Fig 6 (Case 6)—Normal rhythm interrupted by ventricular extrasystoles

DIGITALIS RECORDS

The recent report of Eggleston and Wyckoff⁹ has shown that the approximate total amount of digitalis, when using preparations of standard potency, may be calculated on the basis of one cat unit to 10 pounds (4.5 kg.) of body weight of the patient. The tincture of digitalis was employed in the treatment of the above five patients, and a tincture which has not deteriorated there is one cat unit per cubic centimeter. According to Hatcher and Eggleston¹³ The amount of digitalis indicated, then, may be calculated by the simple procedure of inserting a single decimal point in the figure representing the patient's weight in pounds, for example, if the patient weighs 153 pounds (69.3 kg.), the

13 Hatcher and Eggleston. Observations on the Keeping Properties of Digitalis and Some of Its Preparations, Am J Pharm 85:203, 1913.

approximate amount of the drug is 153 cc H E B Pardee has recorded that the average daily excretion or using up of digitalis when using a tincture of standard potency, is 15 cc Therefore, when the administration of the digitalis is continued, as is usual, over a period of days, an allowance of 15 cc per day should be made for what is used up, the amount remaining, after subtracting 15 cc for each day of the administration from the total amount given, indicates the amount of the tincture of digitalis which may be estimated to be active in the patient at any given time

In another report¹⁴ evidence has been presented which supports the belief that the tincture administered to the foregoing patients was of standard potency It is fully appreciated that there exists some degree of error in arbitrarily using Pardee's average of 15 cc in case the individual patient used up the drug faster or slower (Pardee found 10 and 40 minimis [0.6 cc and 2.5 cc] the extremes) Nevertheless, the method offers a means of estimating the amount of digitalis that was active in the patients at the time of the appearance of the paroxysms of ventricular tachycardia, and it seems worth while to compare this with the amount indicated for full therapeutic digitalization according to the Eggleston method of calculation

The digitalis records of the five patients are given below, they may, perhaps, be more easily visualized by a glance at the table

CASE 1—Body weight, 200 pounds, given 8 cc of tincture of digitalis and then divided doses for 46 days, total amount of digitalis, 50 cc Subtracting 69 cc leaves 431 cc, which is 215 per cent of the 20 cc indicated

CASE 2—Body weight 160 pounds, given 16 cc of tincture of digitalis and then 2 cc from four to six times a day for 53 days, total amount of digitalis 88 cc Subtracting 8 cc leaves 80 cc, which is 500 per cent of the 16 cc indicated

CASE 3—Body weight 135 pounds (before the onset of edema), given 4 cc of tincture of digitalis and then 2 cc in repeated doses for two days, total amount of digitalis 23 cc Subtracting 3 cc leaves 20 cc, which is 148 per cent of the 13.5 cc indicated (The ventricular tachycardia appeared after only 11 cc of digitalis had been given, but there was great probability that the drug had already been administered by the patient's physician before admission to the hospital)

CASE 4—Body weight 190 pounds, given 12 cc of tincture of digitalis and then divided doses until the fifth day, total amount of digitalis, 49 cc Subtracting 6 leaves 43 cc, which is 226 per cent of the 19 cc indicated

CASE 5 Body weight 155 pounds, given 8 cc of tincture of digitalis and then divided doses for five days, total amount of digitalis, 35.3 cc Subtracting 7.5 cc leaves 27.8 cc, which is 179 per cent of the 15.5 cc indicated

As can be seen by these summaries of the digitalis records, or in Table 1, the amounts are well in excess of that estimated for therapeutic digitalization by the Eggleston method The figure of 148 per cent in

14 Reid, W D Some Toxic Effects of Digitalis, J A M A 81 435 (Aug 11) 1923

Case 3 probably does not represent the total amount of the drug which the patient had received.

The patient in Case 3 died from a change of the mechanism to that of ventricular fibrillation, as shown in the electrocardiograms (Fig. 3). The sudden death of the patient in Case 2 during the night was quite possibly of similar nature. This change has been observed by Lewis¹⁵ and others in experimental work on animals, so far as the writer is aware, this is the first record of the event in a human being (that is, the sequence paroxysmal tachycardia of ventricular origin, ventricular fibrillation and death). It is worthy of mention that in both Cases 2 and 3 the clinicians in charge of the treatment continued the administration of the drug after the onset of the regular tachycardia. In Case 1 the drug was temporarily omitted, but after twelve hours a single dose of a digitalis preparation was injected subcutaneously, the regular tachy-

TABLE 1—*Digitalis Records in Cases Reported*

Case	Body Weight in Pounds	Total Digitalis in C c *	Amount Cal- culated by Eggleson Method†	Relation to Course of Digitalis	Number of Days to Digitalis Omitted	Rhythm	Death
1	200	43.1	215%	4.6	No	Persisted	2½ days
2	160	80	500%	5.3	No	Persisted	15 hours
3	135	20**	148%**	2**	No	Persisted	24 hours
4	190	43	226%	4	Yes	Ceased	2 months
5	155	27.8	179%	5	Yes	Ceased	8 days

* After subtracting 1.5 c c per day for the number of days the drug was administered.

** Probably had received digitalis, amount unknown, before admission to the hospital.

† In the discussion of my paper (footnote 14) Dr Eggleson said I should have used the figure 15 cat units per 10 pounds (4.5 kg.) of body weight as I was dealing with the galenical tincture, whereas he employed a purified tincture. Correcting these figures according to Eggleson's suggestion, the percentage relation is found to be 143, 333, 100, 150 and 119 per cent in the five cases, respectively. In my opinion, an overdosage is yet in evidence.

cardia persisted until the death of the patient. In Cases 4 and 5 the prompt discontinuance of the digitalis was followed by recovery from the ventricular ectopic tachycardia, although death resulted later from heart failure.

CONFUSION WITH FLUTTER OF THE AURICLES

In each case the onset of the tachycardia of regular rhythm and fixed rate caused a presumptive diagnosis of auricular flutter to be made, experience with the first case and familiarity with the reports of experimental work enabled me to make the correct diagnosis in the remaining four instances. Of course, resort to graphic methods of examination, preferably an electrocardiogram, was necessary to prove the diagnosis.

In view of what is known of cardiac physiology, it appears unwarranted to believe that the action of digitalis causes the mechanism of

15 Lewis The Mechanism and Graphic Registration of the Heart Beat, New York, Paul B Hoeber, 1920, p 330

auricular fibrillation to change to that of flutter. It is well known that the reverse process, that is, flutter to fibrillation, occurs in a considerable percentage of cases of auricular flutter treated with digitalis, such is an established therapeutic measure. Quinidin sulphate, it is true, often changes auricular fibrillation to flutter, and perhaps this accounts for some of the confusion of thought on the subject. Lewis and his co-workers have clearly demonstrated that the wave is circulating faster in auricular fibrillation than in flutter, averaging 450 in the former and 300 in the latter. T. S. Hart¹⁶ has pointed out that when digitalis is given the auricular waves usually become smaller and more rapid, I have confirmed the acceleration. This fact is in accordance with the extensive data on the mechanism of auricular flutter and fibrillation reported by Lewis and his co-workers in a series of papers¹⁷ published in 1920 and 1921. Lewis¹⁸ has reaffirmed the increase of the auricular rate, that is, the acceleration of the circus movement in flutter and fibrillation of the auricles, by the action of digitalis.

It is because of the clinical resemblance to auricular flutter that it is important that ventricular ectopic tachycardia should be accurately diagnosed. For if the regular tachycardia be thought to be due to flutter of the auricles, the indication would be to give more digitalis with the hope of restoring, as not infrequently happens, the normal rhythm or at least of causing sufficient delay in the auriculoventricular conduction to block some of the auricular impulses and to permit the ventricle to beat at a slower rate. But, if the condition happens to be a tachycardia rising in the ventricle, no amount of A-V heart block will avail, and the further administration of digitalis may prove fatal.

TREATMENT

I am unaware of any successful treatment of ventricular ectopic tachycardia, and this makes the seriousness of the onset of this arrhythmia all the more evident. Vagal stimulation and the injection of atropin in both small and large doses was tried without benefit. Quinidin sulphate might be tried, but it too has caused this rhythm to appear.

The obvious thing to do is to remove the cause, that is, omit the digitalis. Ventricular ectopic tachycardia, in the present state of our knowledge, is better to avoid than to treat.

16 Hart, T. S. Quinidine in Auricular Fibrillation, with Some Observations on Its Use in Combination with Digitalis, *Arch Int Med* **30** 593 (Nov) 1922.

17 Lewis et al. *Heart* **7** 127, 191, 247 and 293, 1920, **8** 37, 83, 141, 171 and 193, 1921.

18 Lewis. The Action of Digitalis in Case of Auricular Fibrillation and Flutter, *Am J M Sc* **164** 157 (Aug) 1922.

SUMMARY AND CONCLUSIONS

Ventricular ectopic tachycardia is a relatively rare arrhythmia

It cannot be differentiated from auricular ectopic tachycardia without an electrocardiogram and not always even then

Previous reports of its occurrence, especially those in which it followed the administration of a drug—chloroform, quinidin sulphate, strophanthin and digitalis—have been mentioned

So far as I am aware, ventricular ectopic tachycardia as a complication of digitalis therapy in man has been previously reported only twice

The histories of five cases in which ventricular ectopic tachycardia appeared during the treatment of auricular fibrillation by digitalis are recorded

In one case the change to ventricular fibrillation was recorded electrocardiographically. This is believed to be the first report in which the electrocardiograms show, in man, the sequence ventricular ectopic tachycardia to ventricular fibrillation

The amount of digitalis administered before the onset of this arrhythmia was well in excess of that indicated by the Eggleston method of calculation

The condition was confused with auricular flutter and more digitalis given to some of the patients

A COMPARISON OF CERTAIN METHODS OF TREATMENT AND DIAGNOSIS OF HOOKWORM INFECTION

W A SAWYER, MD

Assistant Regional Director for the East, International Health Board

AND

W C SWEET, MD

Associate State Director, International Health Board, and Director of the Australian Hookworm Campaign

MELBOURNE AND BRISBANE, AUSTRALIA

The observations presented in this paper were made from Aug 16 to Dec 31, 1922, at the State Hospital for the Insane at Sandy Gallop, Queensland. They are supplementary to the results of an investigation carried out from May 15 to Oct 31, 1922, at the Hospital for the Insane at Goodna, Queensland.¹ In the investigation at Goodna it had been found that patients were being infected with hookworms of the species *Ancylostoma duodenale* and that the infection rates were highest in the wards containing the less teachable insane. The institution was shown to be outside the belt in which there was sufficient rainfall to permit indigenous hookworm infection of the white population not in institutions or mines, but experiments demonstrated that hookworm larvae could develop in the soil in much diminished numbers even under the local winter conditions of moderate rainfall and cool weather. The investigation showed also that carbon tetrachlorid was much less efficient in the removal of *Ancylostoma duodenale* than would have been expected in view of the successes of other investigators using the drug in the treatment of *Necator americanus* infection.

As all the patients at the hospital at Sandy Gallop had been transferred from the hospital at Goodna, it was to be expected that some of them would have an *Ancylostoma duodenale* infection that they had brought with them. On the invitation of Dr A Morrison, medical superintendent, and with his cooperation, and with the approval of Dr H Byam Ellerton, inspector of asylums for Queensland, all the patients in the hospital were examined and the infected ones treated until cured by members of the staff of the Australian Hookworm Campaign. The treatments were so arranged that the efficiency of each method used could be measured by the percentage of worms expelled and by the number of cures.

¹ The work on which this paper is based was conducted with the support and under the auspices of the Department of Health of the Commonwealth of Australia, the International Health Board of the Rockefeller Foundation, and the State of Queensland.

1 Sawyer, W A, Sweet, W C, and Shaw, A E Institutional Hookworm Disease in a Non-Endemic Area, to be published

Sandy Gallop is in the outskirts of Ipswich in southeastern Queensland and lies well inland from the hookworm belt, which is largely limited to the regions of high rainfall along the coast. According to the Commonwealth Meteorologist, the annual rainfall is 34.52 inches, and the greatest amount of precipitation occurs in the summer. The mean temperature for a representative year was 52.9° F. for July, 82.3° F. for January, and 68.5° F. for the year.

The wards of the Hospital for the Insane are supplied with water-flushed closets, and efforts are made to keep the yards as free from soil pollution as possible.

THE PREVALENCE, SEVERITY, AND ORIGIN OF THE INFECTION

Examination of the feces of the 447 patients by the Willis salt flotation method showed that 121, or 27.1 per cent, were infected with hookworms. Seventy-two, or 16.1 per cent, were infected with whipworms (*Trichuris trichiura*), and twelve, or 2.7 per cent, with threadworms (*Oxyuris vermicularis*). No evidence of other intestinal worms was found. As usual, the infection rate for *Oxyuris vermicularis*, as revealed by microscope, was far below the true rate, probably because the ova are deposited low in the large intestine where the contents are no longer liquid. As a result the ova are not mixed throughout the feces and are absent from the majority of fecal specimens taken for microscopic examination. Among 119 patients whose feces were examined after treatment, adult worms of this species were found in eighty-five, or 71.4 per cent.

The 115 female patients in the hospital had a hookworm infection rate of 49.6 per cent, and the 332 males, of 19.3 per cent. The highest rate in any one ward was 63 per cent in Female Ward 1, and the lowest rate, 8.3 per cent in Male Ward 1. All the infected patients were adults, and all but eighteen were of the white race.

That at least the greater part of the hookworm infection had been contracted before the patients were transferred from the hospital at Goodna to the one at Sandy Gallop is suggested by the observation that the number of hookworms harbored decreased with the length of stay. Thirty-four patients who had more than ten hookworms had been at Sandy Gallop an average of 5.6 years, and eighty-five who yielded less than ten hookworms had been there an average of 6.9 years, while 326 persons free from hookworms had been in the institution an average of 8.8 years. Among ninety-two patients who yielded hookworms following treatment, fifty-five who had been in the institution from one to five years had an average of 21.6 worms, twenty-seven who had been there from six to ten years had an average of 18.6 worms, and ten who had been there more than ten years had an average of only 8.3 worms. One patient who had been in the institution nineteen years a period usually considered much longer than

the maximum life of the hookworm, had forty-three hookworms, it would seem probable, therefore, that some infection was being contracted at Sandy Gallop, although it is evident that more hookworms were being lost than gained.

The more frequently the infected patients had gone barefooted, the higher the number of hookworms harbored. The average number of hookworms yielded by fifty-four patients who ordinarily wore shoes was 14.5, while that for thirty-eight who usually went barefoot was 26.2. It is likely that these patients had previously had similar habits when at the hospital at Goodna.

The ninety-two patients who yielded worms after treatment had an average hemoglobin percentage of 73 per cent of the normal by the Tallqvist scale. A representative series of 108 noninfected patients had an average hemoglobin percentage of 75. The ninety-two infected patients yielded an average of 19.3 hookworms each. Since they showed a reduction in their hemoglobin percentage below that of the noninfected controls of about 2 per cent of the normal, the reduction was roughly 1 per cent of the normal for ten worms harbored. These figures are only a rough estimate as the method of testing the hemoglobin could give only approximate results, and the number of observations was small.

The results of the preliminary examinations showed that 27.1 per cent of the patients were infected with hookworms, that the average infection was light, and that most of the infection was contracted before the patients were transferred from the hospital at Goodna to the one at Sandy Gallop.

METHODS OF TREATMENT

Of the 121 patients found to be infected with hookworms, one was too ill to be treated and another developed a fatal attack of lobai pneumonia on the very day of receiving his first dose of the vermicide. The other 119 patients were divided into five groups of approximately twenty-four persons each, and the members of each group were treated according to one of the five methods given in detail in Table 1. The vermicides used were carbon tetrachlorid, oil of chenopodium and the two drugs in combination. Carbon tetrachlorid in doses of 3 c.c. had, in the previous work at Goodna, been found to be relatively so inefficient in removing *Ancylostoma duodenale* that no further tests were made of this drug in the same dosage.

There was no purging or starvation in preparation for treatment. The vermicides were given on an empty stomach, beginning at 6.30 a.m., and the midday meal was given in all cases at 12.30 p.m. The purge given after treatment always consisted of 45 gm. of magnesium sulphate in water. The oil of chenopodium and the carbon tetrachlorid were each given in about one fourth of a glass of water and drunk.

quickly by the patient. The oil floated on the water and the carbon tetrachlorid sank to the bottom, but either was easily taken by this method, which is simpler than inducing insane patients to take drugs in capsules. When both drugs were given together to patients of Group 5 they were mixed just before administration and given with water as described. In the treatment of a few violent patients the use of the stomach tube was necessary.

METHODS OF EXAMINATION

All microscopic examinations were made by the Willis salt-flotation method.² A sample of feces filling about one sixth of a labeled cylindrical, quarter-ounce specimen tin was mixed with a saturated solution of common table salt. The mixture was stirred with a wooden toothpick, while the salt solution was added slowly until the tin was

TABLE 1.—*Plan of Treatments for Hookworm Infection and Methods Used*

Time of Treatment or Examination	Group 1 24 Patients	Group 2 24 Patients	Group 3 23 Patients	Group 4 24 Patients	Group 5 24 Patients
First day, 6 30 a m	1 5 c c oil of chenopodium	0 75 c c oil of chenopodium	5 c c carbon tetrachlorid	10 c c carbon tetrachlorid	0 75 c c oil of chenopodium, 5 c c carbon tetrachlorid
8 30 a m	Purge	0 75 c c oil of chenopodium	A 12 pa- tients	B 11 pa- tients	A 12 pa- tients
10 a m		Purge	Purge	Purge	B 14 pa- tients
Second day, 6 30 a m			Purge	Purge	Purge
First 72 hours	All stools examined for worms				
21st day	Feces of each patient examined by microscope (Willis method)				
22d day	All patients given 2 c c oil of chenopodium, in two doses one hour apart and a purge two hours later				
Next 72 hours	All stools examined for worms				
42d day	Feces of each patient examined by microscope (Willis method)				
43d day	Patients still infected treated with 2 c c oil of chenopodium as before and stools examined for 72 hours for worms				
Thereafter	Three weeks after each treatment the feces were examined microscopically and all patients still infected were treated with 2 c c oil of chenopodium, as before, and the stools were examined for worms for 72 hours. This was continued until all were cured according to the microscopic tests				

just full. A clean, grease-free slide was then laid on the tin so that the surface of the mixture was in contact with the slide. After five or ten minutes the slide was raised and quickly turned over. The upper surface of the adhering pool of water was then examined for floating hookworm ova under the 16 mm objective of the microscope. If no hookworm ova were found, the mixture in the specimen tin was again stirred and another slide applied. If the second preparation failed to show hookworm ova, their absence was recorded.

In examining stools for hookworms the method recommended by Darling, Barber, and Hacker was followed.³ Every stool passed during

2 Willis, H. H. A Simple Levitation Method for the Detection of Hookworm Ova, *Med J Australia* 2:375-376 (Oct 20) 1921.

3 Darling, S. T., Barber, M. A., and Hacker, H. P. Hookworm and Malaria Research in Malaya, Java, and the Fiji Islands, Report of the Uncinariasis Commission to the Orient, Rockefeller Foundation Pub No 9, 1920, p 28-31.

seventy-two hours after treatment was collected and washed through a brass sieve of 60 meshes to the inch. The residue in the sieve was suspended in water in dark photographic trays, and the worms were picked out by painstaking systematic search. They were then put into hot 70 per cent alcohol and set aside for closer identification later.

All the examinations after the first general examination of the institution were made by the same trained microscopist of the Hookworm Campaign. He lived at the hospital during the height of the work, and he planned the treatments so that there would be sufficient time for the numerous laborious worm counts required.

RELATIVE ACCURACY OF THE WILLIS SALT-FLOTATION METHOD AND WORM COUNTS

The Willis salt-flootation method had been shown by several investigators to be more delicate than the direct microscopic examination of water suspensions of feces or of the sediment obtained by centrifuging such suspensions. It had also been found to require less time and less apparatus than the centrifuge method. It remained to be ascertained how this method compared in accuracy with the search of stools for hookworms after a test treatment with an effective vermicide.

As has been shown in Table 1, three weeks after the first round of treatments all the patients in the treatment groups were examined both by the Willis method and by the administration of 2 cc of oil of chenopodium in a divided dose followed by search for hookworms in all stools passed during the subsequent seventy-two hours. This gave an excellent opportunity for a comparative evaluation of these methods of diagnosis.

That 2 cc of oil of chenopodium, as administered in these tests, should remove on an average over 96 per cent of all hookworms present is suggested by the fact that Smillie⁴ removed this percentage of worms by a divided dose of only 1.5 cc of oil of chenopodium given in the same way to a series of fifty-six infected persons. He tested his results against a subsequent dose of 3 cc of oil of chenopodium, divided into three parts given hourly. There was a preliminary purge the evening before this large test dose and another an hour and a half after the last administration of oil of chenopodium. This method of giving 3.0 cc of oil of chenopodium is said to remove on an average 99 per cent of the hookworms present.⁵ As this larger test dose is not infrequently followed by disconcerting symptoms, it seemed preferable

⁴ Smillie, W G. Studies on Hookworm Infection in Brazil, 1918-1920 Second Paper Monographs of the Rockefeller Inst for Med Res, No 17, May 12, 1922, p 68

⁵ Darling, S T., and Smillie, W G. Studies on Hookworm Infection in Brazil First Paper Monographs of the Rockefeller Inst for Med Res, No 14 Feb 1, 1921, p 4

at Sandy Gallop to give 2 cc of oil of chenopodium in test treatments, even if this should necessitate a greater number of treatments and worm counts.

In testing the reliability of diagnoses of hookworm disease made by microscope in the field in Brazil, Darling and Smillie⁶ administered a subsequent test treatment of 3 cc of oil of chenopodium by the method already described, and counted the hookworms expelled. The

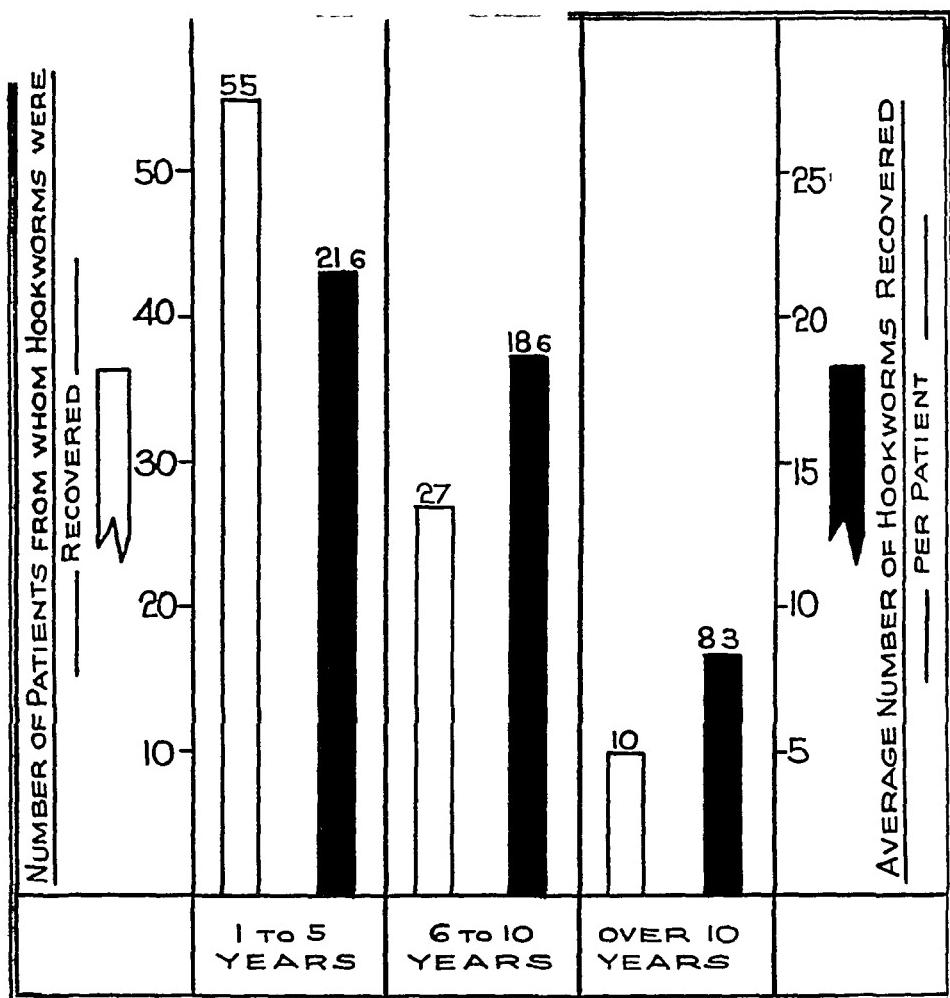


Fig 1.—Relation of the length of stay in the hospital at Sandy Gallop to the number of hookworms harbored.

method which had been used in making the preparations for microscopic examination in the field is not stated, but it is assumed that water suspensions of the feces were centrifuged and examined before the specimens were declared negative, in accordance with the technic in common use in Brazil at the time. The results of these studies in Brazil led Darling and Smillie to the opinion that "The use of microscopic results as an index of the cure of hookworm disease after treat-

⁶ Foonote 5, pp 14 and 15.

ment is of little value and gives a false sense of security”⁶. That this opinion does not hold for the more delicate Willis method of microscopic diagnosis when tested against the search for worms expelled after the moderately less efficient test dose of 2 cc of oil of chenopodium, is shown in Table 2, in which the results at Sandy Gallop are shown and compared with those of Darling and Smillie in Brazil.

It is evident that the Willis method as applied at Sandy Gallop was more accurate as a diagnostic measure than the counting of the worms expelled after a divided dose of 2 cc of oil of chenopodium. The

TABLE 2—Comparisons of the Accuracy of Examination by Microscopic and Worm Count Methods

	Methods Used at Sandy Gallop, Queensland	Methods Used in Brazil (after Darling and Smillie)
Examined by both methods	119	78
Found infected by either method	57	51
Found infected by microscope	55	28
Found infected by worm count	41	48
Percentage discovered by microscope	96.5	54.9
Percentage discovered by worm count	71.9	94.1

TABLE 3—Worms Recovered After Treatment

Group		1	2	3	4	5	Total
Number of persons in group		24	24	23	24	24	119
Number of persons in group yielding hookworms		19	20	19	17	17	92
Ancyllostoma duodenale	Males	80	151	128	146	113	618
	Females	143	272	182	191	213	1,001
	Total	223	423	310	337	326	1,619
Necator americanus	Males	33	0	3	18	1	55
	Females	65	2	4	31	1	103
	Total	98	2	7	49	2	158
Total number of hookworms		321	425	317	386	328	1,777
Average number of hookworms per person treated		13.4	17.7	13.8	16.1	13.7	14.9
Average number of hookworms per person yielding hookworms		16.9	21.3	16.7	22.7	19.3	19.3

greater reliability of the microscopic examinations in Sandy Gallop when compared with those investigated in Brazil is probably largely due to the advantage of the salt-flotation method over the centrifuge method, but it may be partly explained by the advantages of hospital conditions over routine field conditions, especially with regard to the possibility of interchanging specimens.

HOOKWORMS EXPELLED BY TREATMENT

Of the 119 patients included in the treatment groups, ninety-two yielded hookworms after one or more of their treatments. The number, species, and sexes of the worms removed are given in Table 3.

Ten times as many of the hookworms recovered were of the species *Ancylostoma duodenale* as of the species *Necator americanus*, doubtless because the hospital had been infected by hookworms brought from Goodna, where there was a long-standing institutional infection with *Ancylostoma duodenale*. The predominant hookworm of Queensland is *Necator americanus*. Only eight patients among the ninety-two yielded any hookworms of the species *Necator americanus*. In every case all the *Necator* worms were expelled by the first, or trial, treatment.

There were four patients who yielded over 100 hookworms. One patient in Group 1 expelled 103 hookworms, ninety-four of which were *Necator* worms, two in Group 2 expelled 113 and 116 *Ancylostoma* worms, respectively, and one in Group 4 expelled 212 of the *Ancylostoma* species.

TABLE 4.—*Efficiency of the Methods of Treatment*

Vermicide of Trial Treatment	Group	Number of Persons	Cures After Trial Treatment as Shown by Microscopic Examination		Worms Recovered, Subsequent Treatments	Total Number of Worms	Percentage Removed, Trial Treatment
			Number	Percentage			
1 5 cc oil of chenopodium, single dose	1	24	9	37.5	248	73	321
1 5 cc oil of chenopodium, divided dose	2	24	17	70.8	393	32	425
5 cc carbon tetrachlorid	3	23	12	52.2	287	30	317
10 cc carbon tetrachlorid	4	24	15	62.5	370	16	386
0.75 cc oil of chenopodium with 5 cc carbon tetrachlorid	5	24	11	45.8	240	88	328
Total		119	64	53.8	1,538	239	1,777
							86.6

EFFICIENCY OF THE METHODS OF TREATMENT

The efficiency of each of the five methods of treatment was measured in terms of cures and also of hookworms removed by the first or trial treatment. The results are given in Table 4.

The data in Table 4 permit the listing of the methods of treatment in the order of their efficiency as follows:

On basis of cures determined by the microscope (Willis method)

1 15 cc oil of chenopodium in divided dose (Group 2)

2 10 cc carbon tetrachlorid (Group 4)

3 5 cc carbon tetrachlorid (Group 3)

4 0.75 cc oil of chenopodium plus 5 cc carbon tetrachlorid (Group 5)

5 15 cc oil of chenopodium in a single dose (Group 1)

On basis of percentage of hookworms removed (Fig. 2)

1 10 cc carbon tetrachlorid (Group 4)

2 15 cc oil of chenopodium in divided dose (Group 2)

3 5 cc carbon tetrachlorid (Group 3)

4 15 cc oil of chenopodium in a single dose (Group 1)

5 0.75 cc oil of chenopodium plus 5 cc carbon tetrachlorid (Group 5)

The groups of patients were not large enough to give significance to moderate differences between the results from the several methods. The conclusions would seem justified, however, that under the conditions of the tests 10 cc of carbon tetrachlorid and the divided dose of 15 cc of oil of chenopodium were each more efficient than any of the other three methods, that 5 cc of carbon tetrachlorid came next in efficiency and that the single dose of 15 cc of oil of chenopodium and the mixture of 0.75 cc of oil of chenopodium with 5 cc of carbon tetrachlorid were the least efficient. The previous work at Goodna had shown that doses of 3 cc of carbon tetrachlorid were not sufficiently effective to warrant their use in treating *Ancylostoma* infections as only 23.1 per cent of the patients treated by this method were cured, and

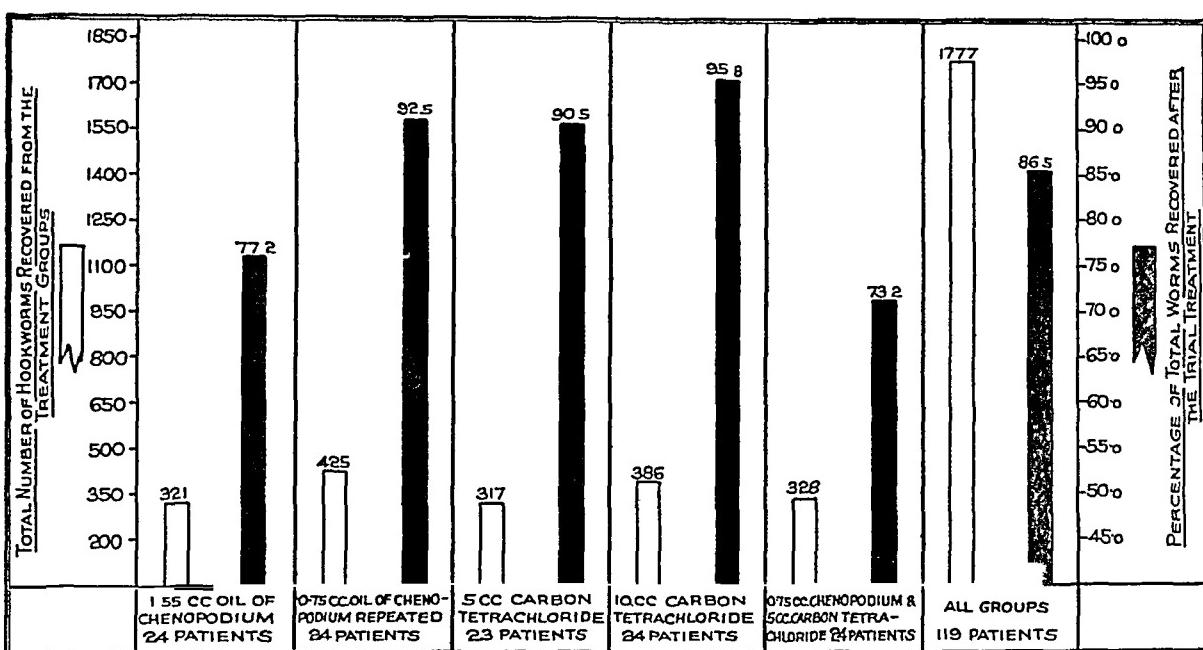


Fig 2.—The total number of hookworms recovered from each treatment group and the percentage recovered after trial treatment

the results were also very poor when measured by worm counts. As the safety of carbon tetrachlorid in doses as large as 5 cc has recently been questioned and has not yet been definitely determined, the best method of those tested at Sandy Gallop for the routine treatment of infections with *Ancylostoma duodenale* would seem to be the divided dose of 15 cc of oil of chenopodium.

EFFECT OF THE PURGATIVE ON THE EFFICIENCY OF CARBON TETRACHLORID

The three groups of patients receiving carbon tetrachlorid were each divided into two subgroups, A and B, as shown in Table 1. Those in subgroup A received the purge 3.5 hours after the vermicide was

given, while those in subgroup *B* were given the purge on the morning of the following day. As shown in Table 5, the results following the early administration of the purge (Subgroups *A*) were the best in all cases, but the differences when carbon tetrachlorid was administered alone (Groups 3 and 4) were not large and may not be significant, considering the small series of observations. The difference was more striking when the mixture of oil of chenopodium and carbon tetrachlorid was given (Group 5), and may have been related to the overcoming of the slight laxative effect of carbon tetrachlorid by the constipating action of oil of chenopodium.

The laxative effect of carbon tetrachlorid was evident when 10 cc of the drug were administered without a purge; five of the twelve patients receiving this treatment had bowel movements within four

TABLE 5.—Effect of the Purgative on the Efficiency of Carbon Tetrachlorid

	Subgroup A				Subgroup B			
	Number of Pa- tients Yielding Worms Recovered	Total Treatment	Worms Recovered, Recovered, of Pa- tients of Hook- Yielding Worms Recovered	Percentage Recovered	Number of Pa- tients Yielding Worms Recovered	Total Treatment	Worms Recovered, Recovered, of Pa- tients of Hook- Yielding Worms Recovered	Percentage Recovered
Group 3 5 cc carbon tetra- chlorid	10	86	82	95.3	9	231	205	88.7
Group 4 10 cc carbon tetra- chlorid	9	279	270	96.8	8	107	100	93.5
Group 5 0.75 cc oil of chen- opodium and 5 cc carbon tetra- chlorid	10	299	231	77.3	7	29	9	31.0
All groups	29	664	583	87.8	24	367	314	85.5

hours, and eight, within six hours. When 5 cc of carbon tetrachlorid were given, only one of eleven patients had a bowel movement within four hours, and a total of seven had one within six hours. The mixture of carbon tetrachlorid with oil of chenopodium had no appreciable laxative effect, none of the ten patients receiving this medication had a bowel movement within four hours, and only two within six hours.

There would seem to be some advantage in giving a purgative after the administration of carbon tetrachlorid as a vermicide.

INQUIRY INTO THE SELECTIVE ACTION OF CARBON TETRACHLORID AGAINST FEMALE ANCYLOSTOMES

On learning of an unpublished observation that carbon tetrachlorid had a marked selective action against female worms in *Necator americanus* infections and differed in this respect from oil of chenopodium, the data collected at Sandy Gallop were analyzed to show the

efficiency of the treatments according to the species and sexes of the hookworms expelled. As all the necators were removed by the trial treatment, they had to be excluded from the comparisons. In Table 6 is shown the percentage of male and female ancylostomes removed by the first, or trial, treatment of each group of patients. It is apparent that, in this series, a slightly larger proportion of male worms than of female worms was removed by the first treatment in every case, and that the differences between oil of chenopodium and carbon tetrachlorid in their slight selective action against the male worms were too small and inconstant to be of significance.

SYMPTOMS FOLLOWING TREATMENT

There seemed to be little choice between the two drugs in the dosage used, so far as symptoms following treatment were concerned.

TABLE 6.—*The Selective Action of Carbon Tetrachlorid and Oil of Chenopodium Against Male Ancylostomes*

Group	Method of Treatment	Total Number of Ancylostomes Removed			Percentage Removed by Trial Treatment		
		Male	Female	Total	Male	Female	Total
1	15 cc oil of chenopodium, single dose	80	143	223	80.0	60.1	67.3
2	15 cc oil of chenopodium, divided dose	151	272	423	93.4	91.9	92.4
3	5 cc carbon tetrachlorid	128	182	310	92.9	88.5	90.8
4	10 cc carbon tetrachlorid	146	191	337	99.3	92.1	95.2
5	0.75 cc oil of chenopodium and 5 cc carbon tetrachlorid	113	213	326	76.1	71.4	73.0
All groups		618	1,001	1,619	89.8	82.4	85.2

The group showing the fewest symptoms was the one which received the smaller dose (5 cc) of carbon tetrachlorid. Doubtless more subjective symptoms would have been reported if the patients had been normal mentally. The symptoms observed are shown in Table 7.

As previously stated, one patient developed acute lobar pneumonia on the very day on which he had received his first treatment for hookworm disease. The vermicide used consisted of 0.75 cc of oil of chenopodium and 5 cc of carbon tetrachlorid, as given to Group 5. The patient was a demented man, 35 years of age, who had been admitted as having alcoholic mania. He died in the evening of the fourth day of his illness. Necropsy was performed by Dr Morrison, superintendent of the hospital. Nothing of special interest was found beyond various stages of gray and red hepatization of the entire left lung and engorgement and early red hepatization of the lower and middle lobes of the right lung. The liver was not enlarged but appeared somewhat granular and light in color. There was cloudy swelling of spleen and kidneys. A specimen of tissue from the liver

was sent to Dr J V Duhig, pathologist in Brisbane, and he reported that the cells of the lobules, more especially about the portal zone, appeared faintly cloudy with blurring of their nuclei, changes which might be due to the acute illness. No signs of fat necrosis were noted.

CONTROL MEASURES

At the conclusion of the investigation it was recommended that all patients before transfer from the hospital at Goodna to the one at Sandy Gallop be examined for hookworm disease, and cured if infected, that locked boots be worn by all patients who cannot otherwise be kept in boots while in the yards, that the strictest possible watch be

TABLE 7.—*Symptoms Observed After Treatment*

Group	Drug and Dose	Treated	Number of Patients			Comments
			Vomiting	Feeling Sick	Appearing Drowsy	
1	15 cc oil of chenopodium, single dose	24	6	0	0	
2	15 cc oil of chenopodium, divided dose	24	6	0	0	
3	5 cc carbon tetrachlorid	23	2	0	0	
4	10 cc carbon tetrachlorid	24	6	1	2	1 case of persistent vomiting for 48 hours
5	0.75 cc oil of chenopodium and 5 cc carbon tetrachlorid	24	6	1	1	
Test treat	2 cc oil of chenopodium, divided dose	119	17	2	0	1 case of persistent vomiting for 48 hours

maintained to keep the yards free from soil pollution, and that the patients be examined yearly for hookworm infection and treated if infected.

CONCLUSIONS

1 In doses at present regarded as sufficiently safe for use on a large scale in the field, carbon tetrachlorid is not as efficient as oil of chenopodium in the treatment of infections with hookworms of the species *Ancylostoma duodenale*.

2 Oil of chenopodium in a dose of 15 cc, given in two equal parts at an interval of two hours and followed by a purge, proved highly efficient and was superior to the undivided dose.

3 The Willis salt-flotation technic of microscopic examination of feces is a simple and efficient test of the presence of hookworm infection, and compares well, as a method of determining cures, with the search for hookworms expelled after safe doses of oil of chenopodium.

4 Carbon tetrachlorid is a mild laxative, but it cannot be depended on to move the bowels when used in moderate doses or mixed with oil of chenopodium. It would seem good practice to give a purge three or four hours after the administration of this drug.

CLINICAL RESULTS OBTAINED WITH BACILLUS ACIDOPHILUS *

NICHOLAS KOPELOFF, PH D

WARD'S ISLAND, NEW YORK

Bacillus acidophilus has been used successfully in the treatment of constipation and diarrhea¹. However, it would be difficult to state precisely how successful a therapeutic agent it is. Neither of the intestinal conditions dealt with—constipation and diarrhea—permits exact definition, consequently, the interpretation of results must be somewhat arbitrary. For this reason, if no other, it would seem desirable that investigators in this field present their facts as objectively as possible. Obviously, there are many factors which must be considered. The necessity for keeping a careful record of the frequency and character of defecations is well recognized. The dosage of *B. acidophilus* preparations is always of importance, but unfortunately it is unstandardized and therefore at present has little significance. Thus 10 cc of *B. acidophilus* milk containing 20,000,000 viable organisms per cubic centimeter in the hands of one clinician is unquestionably more desirable than 1,000 cc containing 10,000 viable organisms per cubic centimeter when administered by another. Since the transformation of the intestinal flora from the proteolytic to the aciduric type appears to depend on a mass inoculation, the importance of ingesting large numbers of viable *B. acidophilus* cannot be overemphasized. It is common experience that frequently in treating severe cases of chronic constipation it is necessary to increase the dose before obtaining beneficial results. We have given as much as 1,500 cc of *B. acidophilus* milk and 400 gm of lactose daily in some instances before alleviating the constipated condition. Another practice that has proved valuable in difficult cases is the use of a high enema of *B. acidophilus* milk, thinned with a small amount of warm water. Generally these enemas are advised on two or three successive days. It is likely that in cases reported as failures, a sufficient increase in the number of viable organisms administered might have resulted in success. In this connection it may also be stated that the chief criticism against the commercial preparations of *B. acidophilus* now on the market is that the number of viable organisms they contain is too small to yield satisfactory results when compared with the mass inoculation.

* From the department of bacteriology, New York State Psychiatric Institute

¹ Kopeloff, N. Is the Action of *Bacillus Acidophilus* a Strictly Bacteriologic Phenomenon? J A M A 80 602-604 (March 3) 1923 Rettger, L F, and Cheplin, H A. The Intestinal Flora, Yale University Press, 1921

lations made by scientific investigators. It is unfortunate, therefore, that the commercial products examined cannot bear recommendation.

It is not only important to study the influence of *B. acidophilus* on the intestinal condition as compared with the period immediately preceding treatment, but also to note how long any changes which have been induced persist. In previous communications these facts have been indicated, and the present report is concerned with the continuation of such an investigation. The female psychotic patients under treatment for constipation were twenty-seven in number, in addition to which there were also three mentally normal subjects. Two more subjects, one of them psychotic, were under treatment for diarrhea. The procedure and technic have been described elsewhere. The *B. acidophilus* milk which was administered varied from 110,000,000 to 440,000,000 viable organisms per cubic centimeter, with an average of about 200,000,000 per cubic centimeter. Recent radiographic examination to determine intestinal motility in some of the patients caused them to be divided into two equal groups showing atonic and spastic constipation.

In Table 1 are included the results of the treatment of constipation and diarrhea with *B. acidophilus* milk. It will be seen that this table has been so arranged as to show three periods. Before treatment, during treatment and after treatment. Under each period there are two columns, the second showing the number of days of observation, the first showing the number of days during which the normal defecations occurred. More than one normal defecation per day has been counted as only one defecation so as not to confuse the main consideration. The period after treatment has been divided into two parts, the first, to show the effect of continuing the ingestion of lactose alone, the second, comparable to the period before treatment. The final column of "Remarks" indicates the reasons for discontinuing treatment. Whenever this is blank, it is to be understood that observations are being continued.

If the data for patients 1 to 7 are examined in some detail, it will be seen that without exception there has been a significant increase in the number of defecations during treatment with *B. acidophilus* milk and lactose as compared with the period before treatment. In several instances this is striking, when the severity of the constipation is considered. Thus patients 1, 3, 4 and 6 had one defecation per week or less before treatment and three or more defecations per week during treatment. Patients 1, 2 and 5 had almost daily defecations during treatment. Patient 8 was disturbed throughout the treatment, frequently refusing and sometimes spilling the milk. She has failed to respond to treatment which has not been as intensive as desired. While it is not feasible to include all the data concerning the amount

and character of the feces of the patients under observation, in almost every instance there has been recorded an increase in the amount of feces as well as a change in color and consistency. The feces usually became lighter in color and much softer in consistency. Patients 9 to 12 are of special interest since they have been given lactose alone following the period during which they received *B. acidophilus* milk.

TABLE 1.—*The Influence of B. Acidophilus Milk on Constipation and Diarrhea*

Number	Name	Before Treatment		B. Acidophilus Milk + Lactose		After Treatment				Remarks	
						Lactose		Nothing			
		No. of Normal Defecations	No. of Days	No. of Normal Defecations	No. of Days	No. of Normal Defecations	No. of Days	No. of Normal Defecations	No. of Days		
1	K Hv	2	14	51	62			32	38	Too disturbed	
2	M Kv	17	73	59	61			195	270	Paroled	
3	L R	11	103	13	27			236	341		
4	M Cn	0	7	52	100			42	61	Paroled	
5	M Hv	95	116	38	39			133	137	Paroled 100 days	
		3	27	1	7					Continued	
6	S Fz	1	34	67	99			24	84	Discontinued	
		0	10	34	49					Continued	
7	S Sr	12	19	16	18			129	169	Paroled	
8	R Sn	12	18	32	61			40	100		
9	G Et	8	31	41	62	57	70	34	37	Too disturbed	
10	M Et	1	7	47	50	74	124	2	44	Childbirth	
11	R Rr	4	28	17	22	56	60	3	6		
						12	14			Paroled	
12	M Hn	49	92	109	189	57	119	29	54		
13	M Fd	1	14	55	101					Illness	
14	M Hw	1	12	26	48					Paroled	
15	K Rb	0	14	93	175					Continued	
16	M Fr	2	25	16	22					Paroled	
17	A Dz	5	47	42	86					Paroled	
18	E Sh	21	64	5	7					Too disturbed	
19	E Bt	19	45	17	49					Continued	
20	E Hh	2	7	14	17*			27	39		
21	A Hn	1	6	7	18*			6	27	Too resistive	
22	C Sn	3	7	41	49*					Continued	
23	I Gr	3	15	42	61*					Continued	
24	A Br	3	15	30	62*					Continued	
25	B Sn	3	27	6	14*					Continued	
26	S Shr	0	28	0	14*					Continued	
27	A Sy	0	16	5	14*					Continued	
Normal Subjects—Constipation											
28	M Wr	5	30	53	56	66	66	89	89		
29	H Wn	4	30	106	120	46	46	43	64	Continued	
30	J Hn	8	14	38	38			7	7		
Diarrheal Subjects											
31	M Kz	234	39	37	23					Discontinued	
32	W Kt	135	27	74	36					Discontinued	

* B. acidophilus milk but no lactose

and lactose. This was done in order to determine whether the beneficial effects of *B. acidophilus* could be prolonged by supplying carbohydrate in sufficient quantity for bacterial development. It will be seen that Patient 9 had forty-one defecations in two months while receiving *B. acidophilus* and lactose, and on lactose alone she had fifty-seven defecations in a slightly longer period, indicating that the beneficial effect persisted for at least this length of time. For a little over a month following this, during which feeding of lactose was stopped,

this patient continued to have almost daily defecations as compared with eight defecations per month in the period of observation preceding treatment Patient 10, who had only one defecation in the week preceding treatment and then had forty-seven defecations in fifty days while receiving *B. acidophilus* and lactose, continued favorably for four months when taking lactose alone However, when the lactose administration was discontinued, she became severely constipated again Practically the same course was run by Patient 11 Patient 12 usually responded to treatment, although the figures here presented, 109 defecations in 189 days while receiving *B. acidophilus* and lactose, do not indicate that for the last two months of this six month period she had fifty-seven defecations in sixty-four days However, when *B. acidophilus* was discontinued, a retrogression to her original condition occurred From an analysis of these few cases it seems likely that the beneficial effects of *B. acidophilus* treatment can be prolonged by the use of lactose, even after the ingestion of viable organisms has stopped The alternative explanations thus suggested are first, that the lactose furnishes a suitable medium for the development of *B. acidophilus* in the intestine and perpetuates the transformation of the intestinal flora, or second, that the lactose alone is responsible for the relief of constipation While it is generally accepted that lactose has laxative properties, nevertheless its use has never been accompanied by such uniformly good results as have been obtained with *B. acidophilus* In order to obtain further data along these lines, there has been included in Table 1 a series of Patients 13 to 19 who have received *B. acidophilus* milk and lactose as against another series—20 to 27—who have received *B. acidophilus* alone Patients 13 to 18 showed a striking increase in the number of defecations while receiving *B. acidophilus* milk and lactose as compared with the period before treatment Thus, Patients 13 to 17, who had about one normal defecation in two weeks before treatment, had a defecation every other day after treatment Patient 19 is still receiving treatment because of her failure to respond As might be expected the normal subjects, 28 to 30, yielded results identical with those obtained with psychotic patients Patients 20 to 27 have received *B. acidophilus* milk without lactose Here again there is a striking increase in number of defecations during treatment as compared with the preceding period of observation The last three patients—25 to 27—have received treatment only two weeks and therefore cannot be expected to show such marked improvement A comparison between the patients receiving *B. acidophilus* milk and lactose and those receiving lactose alone leads to the conclusion that the beneficial effect of *B. acidophilus* treatment depends rather on the viable organisms than on the laxative properties of the lactose In fact Rettger and Cheplin in their comprehensive investigation have estab-

lished the relative value that attaches to the feeding of *B. acidophilus* with and without different sugars, and these data corroborate their findings.

There remain the diarrheal subjects still to be considered. The first of these, Patient 31, was psychotic. She averaged approximately six defecations a day. All medical efforts to alleviate her condition were without avail. On treatment with *B. acidophilus* milk without lactose the number of defecations was greatly reduced, and for the last week of treatment she had only one defecation a day. The other subject, No. 32, presented a similar condition in lesser degree, and was soon benefited.

One of the most important questions which arises in connection with the therapeutic value of *B. acidophilus* is whether the relief obtained from constipation and diarrhea is permanent or merely transitory. From the data presented in Table 1 there is no doubt that the beneficial effects of *B. acidophilus* are in evidence so long as the treatment is in progress. However, if attention is directed to the period following treatment when neither *B. acidophilus* nor lactose was ingested some interesting facts are disclosed. With the exception of two cases, those of Patient 8, who never fully responded to treatment and Patient 12, the number of normal defecations in the period following treatment has been greater than in the period before treatment. The length of time of the period following treatment is of significance in interpreting these results. It has varied from six to 341 days. For a period of less than three months following treatment the beneficial effects have persisted in all but one instance. The cases of the four patients who have been observed for more than four months following treatment are worthy of a detailed account. Patient 2 has had 195 defecations in 270 days following treatment. During the thirty days preceding the writing of this paper this patient had twenty-seven normal defecations eight months after treatment. However, it must be mentioned that the amount of feces excreted has diminished perceptibly, so that this patient has been advised to take lactose. Patient 3 has had 236 defecations in 341 days following treatment, as compared with eleven in 103 days preceding treatment. During thirty days, nine months after treatment, she had sixteen defecations. Patient 5 had 133 defecations in 137 days following treatment, as compared with ninety-five defecations in 116 days preceding treatment. Following a gynecologic operation and her parole of three months, she became severely constipated. The last subject, Patient 7 had 129 defecations in 169 days following treatment, twenty-three in the thirty days preceding the writing of this paper.

In general, then, it may be stated that the beneficial effects of *B. acidophilus* have persisted for a considerable period of time sub-

sequent to treatment, in fact, for more than eleven months. However, it must be recognized that there is a perceptible tendency toward diminution in the amount of feces excreted. This might be favorably influenced by the continued use of lactose, as has been indicated. Thus, the improvement in Patients 9, 10, 11 and 12, who took lactose from two to four months following the ingestion of *B. acidophilus* was retained in a satisfactory manner.

TRANSFORMATION OF INTESTINAL FLORA

The transformation of the intestinal flora is an important consideration in *B. acidophilus* therapy. As has been already stated, a weekly microscopic examination of the feces has been made, and the relative percentage of gram-positive and gram-negative bacteria recorded. Further, the feces have been plated on whey agar and the percentage of *B. acidophilus* colonies reported. Because of the space that would otherwise be required, these data have been summarized in Table 2. A final column has been added showing the number of days during which one or more normal defecations occurred in the thirty days subsequent to the time the bacterial counts indicated were made. It should be stated that the highest percentage of gram-positive bacteria generally occurred simultaneously with the highest percentage of *B. acidophilus* colonies on the plates, but this was not invariably the case. The number of defecations is recorded for the thirty days following the highest microscopic count of gram-positive organisms.

There are several interesting facts revealed in Table 2. The most important of these is that the highest percentage of gram-positive bacteria in the feces is an almost certain index that the number of normal defecations will be highly satisfactory subsequently for at least thirty days. Thus, with the exception of Patient 6, who received no treatment following the highest count, Patient 8, who was too disturbed to react favorably, and Patient 27, who in twenty days failed to respond to treatment, all of the cases averaged two or more defecations in three days. Many of these had almost daily defecations. It should be remembered that most of these patients suffered from severe constipation prior to treatment. (Twelve of the twenty-two patients recorded had one defecation or less per week, and the remainder did not have many more.) These figures point directly toward the conclusion that the transformation of the intestinal flora is responsible for the improvement of the patients under consideration. A detailed examination of the data in Table 2 again shows that the highest microscopic counts of gram-positive bacteria fall considerably below 100 per cent. In fact, 85 per cent is the highest figure recorded. About two thirds of the counts are above 50 per cent, as compared with an average count of about 16 per cent of gram-positive bacteria before

treatment. The microscopic counts and the plate counts are not in good agreement, for in half the cases the microscopic count is higher than the plate count, and vice versa, due to the presence of dead bacteria in the microscopic count. It is interesting, however, to note the condition of the patients showing 100 per cent of *B. acidophilus* in their feces, namely, Patients 13, 22, 23 and 24. The first three of these had practically daily normal defecations, while the last did not respond so perfectly to treatment. This again indicated that a transformation of the intestinal flora to the acidophilic type is responsible for an increase in the number of normal defecations. It is of interest in this connection to mention again the fact that in three patients, namely,

TABLE 2.—Relative Percentage of Gram-Positive Bacteria in Feces

Number	Name	Highest Percentage of Gram-Positive Bacteria		Number of Normal Defecations for Succeeding 30 Days
		Microscopic Percentage	Plate Percentage of <i>B. Acidophilus</i>	
1	K Hv	53	94	26
2	M Kv	68	+	30
3	L Rh	78	+	27
4	M Cn	35	+	22
5	M Hy	64	70	29
6	S Fz	80	50	11**
7	S Sr	37	4	26
8	R Sn	70	80	14
9	C Et	85	85	25
10	M Lt	62	50	23
11	R Rr	78	11	30
12	M Hn	52	50	29
13	M Fd	55	100	28
14	M Heu	48	98	21
15	K Rb	85	65	20
16	M Fv	39	15	11 in 17 days
17	A Dz	70	3	
18	E Sh	16	*	13 5 in 7 days
19	E Bt	Record incomplete		
20	E Hh	Record incomplete		
21	A Hn	Record incomplete		
22	C Sn	54	100	16 in 17 days
23	I Gr	43	100	
24	A Br	37	100	15
25	B Sn	Record incomplete		
26	S Sh	Record incomplete		
27	A Sv	34	0	6 in 20 days

* Not counted

** Discontinued treatment

Patients 3, 5 and 12, there were recovered from the feces viable *B. acidophilus* in considerable number six months after treatment had been discontinued.

COMMENT

Any interpretation of the results of this investigation must take into consideration its inherent difficulties. As stated at the outset, a discussion of constipation involves arbitrary standards. While the number of subjects has been limited, the effort has been made to study them in such a way as to make comparisons valid. In any event the obvious benefits obtained by the use of *B. acidophilus* in cases of constipation and diarrhea can scarcely be questioned. A discussion of the mechanism of its action is reserved for another communication.

SUMMARY

1 A series of thirty constipated subjects were under observation before, during and after treatment with *B. acidophilus*. A comparison of these periods shows that during treatment the number of normal defecations was significantly increased.

2 The beneficial influence of *B. acidophilus* usually persists for a considerable period of time after treatment has been stopped. Patients have been observed for from one week to about one year after treatment, and almost without exception all have had more normal defecations after than before treatment.

3 The use of lactose during and after ingestion of *B. acidophilus* does much to enhance the beneficial effects.

4 A transformation of the intestinal flora from a proteolytic to an aciduric type as shown by microscopic and plate counts may generally be induced. Such transformation is usually accompanied by almost daily defecations regardless of the severity of the constipation.

5 Two cases of diarrhea have been successfully treated by the ingestion of *B. acidophilus*.

STUDIES ON THE NATURE OF BACILLUS ACIDOPHILUS THERAPY¹

NICHOLAS KOPELOFF, PH.D., AND PHILIP BEERMAN
WARD'S ISLAND, NEW YORK

The relief obtained from constipation and diarrhea by the use of *B. acidophilus* has been interpreted in several ways. In previous communications¹ it has been shown that the action of *B. acidophilus* milk is neither strictly physical nor chemical, that is, does not depend upon volume or chemical constituents, but appears to be essentially a bacteriologic phenomenon. This conclusion was based on the fact that neither sterile skim milk nor sterilized *B. acidophilus* milk influenced constipation, as did *B. acidophilus* milk in which the viable organisms were uninjured. The foregoing experiments were open to some criticism on the ground that sterilizing *B. acidophilus* milk caused a change in chemical composition. This study was therefore extended along somewhat different lines.

In order to feed *B. acidophilus* milk in which the viable organisms were eliminated, the following procedure was adopted. *B. acidophilus* milk prepared in the usual way was centrifuged, and the supernatant liquid was put through a Mandler diatomaceous filter. The labor involved was time consuming. It was through the courtesy of Dr. Charles Kuumwiede, assistant director of the Research Laboratories of New York City Health Department, that we were able to use a Sharpless supercentrifuge, which greatly facilitated the preliminary work. The liquid was then run through a "Vaccu-Filter," a coarse Mandler diatomaceous filter, and finally through a fine Mandler filter. This filtrate was always tested for sterility on whey agar plates and was fed to patients as "bacillus acidophilus filtrate," 900 cc per day. This amount is roughly equivalent to the liquid portion of 1,000 cc of regular *B. acidophilus* milk. An attempt was made to feed the residue from the supercentrifuge which contained viable *B. acidophilus* organisms, for comparison with the filtrate, but, unfortunately, the supply was not continuous, and therefore the results were inadequate. In stating in our previous communication the results of feeding sterilized *B. acidophilus* milk, mention was made of the fact that the acidity of *B. acidophilus* milk was neutralized prior to sterilization. This procedure obviously affected the lactic acid content. Consequently, in

* From the Department of Bacteriology, New York State Psychiatric Institute, Ward's Island, New York City.

¹ Kopeloff, N. Is the Action of *Bacillus acidophilus* a Strictly Bacteriologic Phenomenon? J. A. M. A. 80: 602-604 (March 3) 1923. Clinical Results Obtained with *B. acidophilus* Milk, Proc. Soc. Exper. Biol. Med., May 16, 1923.

continuing the feeding of sterilized milk in the present study, chemically pure lactic acid was added to sterilized *B. acidophilus* after sterilization in an amount equivalent to the acidity as previously titrated by twentieth normal sodium hydroxide. In accordance with the general plan of our *B. acidophilus* studies, the subjects were psychotic patients, numbers thirty-five to thirty-eight being male and the others female. Observations as to daily defecations were recorded prior to treatment.

In Table 1 are presented the results as obtained with *B. acidophilus* milk prepared in the manner described above. Considering first the influence of "*B. acidophilus* filtrate" on constipation, it will be seen that in general there is little, if any, difference in the relative number of normal defecations in the period during which *Bacillus acidophilus* filtrate was ingested as compared with the period before treatment.

*The Influence on Constipation of *B. Acidophilus* in Various Forms*

Number	Name	Before Treatment		Sterilized <i>Bacillus Acidophilus</i> Milk + Lactic Acid		<i>Bacillus Acidophilus</i> Filtrate		<i>Bacillus Acidophilus</i> Milk	
		Number of Daily Defecations*	Number of Days	Number of Daily Defecations	Number of Days	Number of Daily Defecations	Number of Days	Number of Daily Defecations	Number of Days
25	B Sn	2	25			1	21	9	21
27	A Sy	0	15			2	21	6	21
33	K Sa	11	31			5	14		
34	M Bt	0	5			0	13		
6	S Fz	5	35	2	14	6	36	13	24
19	E Bt	12	35	6	21	16	38	7	23
35	E Cy	6	19	8	21	8	22	10	21
36	S Ms	13	21	17	21	16	22	19	22
37	A Jn	5	17	14	21			17	23
38	H Gn	6	17	9	21			11	21
39	J Qn	10	16	16	21			12	21

* Normal

This is to say, that the chemical constituents of *B. acidophilus* milk, including the acid reaction, are not effective in alleviating constipation. Neither does the physical factor of volume exert much influence, since the patients received 900 c.c. of *Bacillus acidophilus* filtrate daily. The patients were subsequently given regular *B. acidophilus* milk, and it will be seen that with one exception all patients showed some increase in the number of normal defecations. This is not as striking as might perhaps have been anticipated, but it must be remembered that the patients had been permitted to become extremely constipated before obtaining *B. acidophilus* milk. Furthermore, the beneficial effects of *B. acidophilus* are ordinarily greatly enhanced by lactose which was not given in the present instance in order to avoid complicating the interpretation of results. These data, therefore, lend further support to the conclusion that *B. acidophilus* therapy is more strictly bacteriologic than it is chemical in nature. It is manifest that any bacteriologic phenomenon may be regarded as biochemical in character, and conse-

quently that of *B. acidophilus* is no exception. We have tried to determine where the chief emphasis belongs. Are the laxative qualities of *B. acidophilus* milk due mainly to the physical factor of volume? We have shown that this is not the case. Are they due to the chemical constituents elaborated by bacteria? These experiments would tend to disprove that contention. Are they due chiefly to the transformation of the intestinal flora as here indicated, and therefore essentially bacteriologic in nature? Further evidence of this may be found in data presented elsewhere, namely, that the beneficial effects of *B. acidophilus* persist for a considerable period of time after discontinuing treatment. Also it is important to note that viable *B. acidophilus* organisms have been recovered from the feces of patients six months after discontinuing treatment.

Again, when the results of feeding sterilized *B. acidophilus* to which lactic acid has been added, are considered, it will be seen that there is little evidence of any relief of constipation during this period as compared with the period before treatment. The physical factor of an increased volume was present of course. However, when regular *B. acidophilus* milk was added to the diet, in all but one instance an increase in the number of normal defecations was noted. While this increase is not striking, when all the facts are surveyed they again indicate that it is a bacteriologic rather than a chemical interpretation that will account for the action of *B. acidophilus*.

It has been shown how *B. acidophilus* affects elimination from the human intestinal tract, but the reason for this is a more difficult problem. The results here reported are to be regarded rather as suggestive than as final, since the studies are still in progress. However, there seems to be a sound basis for considering that *B. acidophilus* therapy is essentially bacteriologic in nature.

SUMMARY

1 In order to study the influence of physical and chemical factors, *B. acidophilus* milk was centrifuged and run through a Mandler diatomaceous filter. Thus the chemical constituents were little altered. When fed to constipated patients it was practically without effect. Regular *B. acidophilus* milk ingested subsequently resulted in an increase in the number of normal defecations.

2 *B. acidophilus* milk was sterilized and lactic acid added, thus again approximating the original chemical composition. When fed to constipated patients, little change was noted. Regular *B. acidophilus* milk ingested subsequently resulted in an increase in the number of normal defecations.

3 These data indicate that *B. acidophilus* therapy is essentially bacteriologic rather than physical or chemical in nature.

DISTURBANCES OF RENAL FUNCTION IN PERNICIOUS ANEMIA *

EDWARD J STIEGLITZ MS, MD
CHICAGO

In pernicious anemia there is frequently evidence of mild renal damage, manifesting itself by albumin, casts or both in the urine. Up to the present time it has been assumed that this renal irritation or damage is a result of malnutrition and anoxemia of the kidneys because of the anemia. On the other hand, the incidence of albuminuria and other clinical evidence of renal disturbance is low in cases of secondary anemia. The hemolytic intoxication of pernicious anemia may also injure the kidneys directly, but it has long been known that in pernicious anemia there is a superabundance of "free" or inorganic ionizable iron in the blood and tissues. That the deposition of iron in the kidneys may cause mild nephritic changes in experimental animals was demonstrated several years ago.¹ The presence, therefore, of renal hemosiderosis might be responsible for the renal disturbance in pernicious anemia. It was with this in mind that the following investigation was undertaken. The problem will be discussed along the following lines: the incidence of renal damage in pernicious anemia, its clinical and functional characteristics, the pathologic nature of this renal disorder, especially the presence, nature and degree of renal hemosiderosis, the effect of the deposition of iron in the kidney on renal function, and lastly, the correlation of these data.

The incidence of renal disturbance of a mild degree in pernicious anemia is high. Cabot² gives a 46 per cent incidence of albuminuria in 506 cases of pernicious anemia. In fifty cases which have now been compiled from the records of Johns Hopkins Hospital, thirty-one, or 62 per cent, showed urinary albumin, casts, or both. In 100 cases from the Presbyterian Hospital, Chicago, 57 per cent gave the same indication of renal impairment. The average incidence in these several groups is 50 per cent. On the other hand, in 100 cases of secondary anemia associated with a great variety of diseases from the Presbyterian Hospital, Chicago, albuminuria was present in only 14 per cent. And of these fourteen, four had nephritis or lesions of the urinary tract which were major factors in producing the anemia. The difference in the occurrence of albuminuria in the two types of anemia is striking.

* From the Department of Medicine, Johns Hopkins Hospital Baltimore

1 Stieglitz Am J Anat 29 33, 1921

2 Cabot in Osler and McCrae Modern Medicine, Philadelphia, Lea & Febiger 4, 628

The average age of patients suffering from pernicious anemia with albuminuria is the same as for those without, but the group showing albuminuria show, on the average, a lower hemoglobin percentage than the group with negative urine findings. The average hemoglobin content of the blood for the 150 cases of pernicious anemia was 41 per cent, the average of the albuminuric cases was 36 per cent and for those without albumin 46 per cent. The significance of this fact will be discussed later.

The clinical character of the renal disturbance has been studied by many, notably Christian,³ Mosenthal⁴ and Tileston and Comfort⁵. As far back as 1898 Alburt⁶ described a rather fixed, low urinary specific gravity in connection with this disease. Essen and Porges⁷ report twelve cases of pernicious and secondary anemia in which the renal disturbance became severe when the hemoglobin of the blood fell below 30 per cent, the kidneys then functioning with a minimum of effort. Christian,⁸ working with the Mosenthal⁹ modification of the dietary test for renal function first suggested by Hedinger and Schlayer¹⁰ studied the renal function in fourteen cases of pernicious anemia. He found that the renal function as evidenced by the ability of the kidney to concentrate the urine and respond to diuresis was similar to that found in chronic nephritis. The fixation of the urinary specific gravity was most marked when the hemoglobin was low, and if the anemia had persisted for a long time permanent renal impairment might occur. Christian suggested that this disturbance of the ability of the kidney to concentrate the urine was due to the anemia, and depended on nutritional deficiency or toxic disturbance. The phenolsulphonephthalein secretion was found to be about normal. This finding was confirmed by others. Mosenthal¹¹ gave exactly similar findings with the test that bears his name. On the other hand, Cabot¹² makes no mention of renal disorder in his studies of pernicious anemia.

³ Christian, H A Renal Function in Anemia, Arch Int Med **18** 429 (Oct) 1916, Boston M & S J **174** 656, 1916

⁴ Mosenthal, H O Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine, Arch Int Med **16** 733 (Nov) 1915. Mosenthal, H O, and Lewis, D S A Comparative Study of Tests for Renal Function, J A M A **67** 933 (Sept 23) 1916.

⁵ Tileston, W., and Comfort, C W The Total Non-Protein Nitrogen and the Urea of the Blood in Health and Ill Disease, as Estimated by Folin's Methods, Arch Int Med **14** 620 (Nov) 1914

⁶ Coupland, Sidney, in Alburt System of Medicine, 1898

⁷ Essen and Porges Wiener Arch f inner Med **5** 195, 1922

⁸ Christian, H A Arch Int Med **18** 429 (Oct) 1916

⁹ Mosenthal Arch Int Med **16** 733, 1915

¹⁰ Hedinger and Schlayer Deutsch Arch f klin Med **64** 120, 1914

¹¹ Mosenthal J A M A **67** 933 (Sept 23) 1916

¹² Cabot Am J M Sc **120** 139, 1900

Urobilin in increased quantities in the urine has frequently been described. The mechanism of the formation of urobilin is still in doubt,¹³ but it is increased in any disease in which hemolysis is exaggerated.¹⁴ Kahn and Barsky¹⁵ report that there is relatively little alteration in the phenolsulphonephthalein test of Rountree and Geraghty.¹⁶

Our own results confirm these findings in six cases studied by the Mosenthal test, while eighteen phenolsulphonephthalein tests gave an average secretion of 65 per cent of the dye in two hours. As Christian⁸ points out, the fixation of the specific gravity and the increase of the night over the day volume of urine was noted as being most marked in the cases with the most marked anemia. The only abnormal finding in the blood chemistry of these cases was a uniform but slight increase in the uric acid content. The average in five cases was 42 mg per 100 c.c. of blood, varying from 396 to 442. The nephritis of pernicious anemia is rarely, if ever, of such a degree as to be a marked factor in the prognosis.

The significance of the fixation of the specific gravity and the retardation of water elimination is particularly important in connection with the effects of iron deposition in the renal cells as discussed in a previous paper¹ and further elaborated in this.

The pathologic aspect of the renal changes of pernicious anemia that have been described clinically, is not so clear. No uniform pathologic changes are found grossly in the kidney at necropsy. In the protocols from the pathologic laboratory, Johns Hopkins Hospital, of necropsies of thirty-six cases of pernicious anemia, 83 per cent of the cases showed a renal pathologic condition. The most common and uniform finding was tubular degeneration, often fatty in character, which occurred in 53 per cent of all the cases. In 42 per cent of the cases there was a gross renal hemosiderosis. The presence or absence of iron was not mentioned in the protocols of 44 per cent of the cases, as no special search was made for iron at the time. The actual incidence of slight or microscopic hemosiderosis must be higher, especially in

13 Bauman, L. Chemistry and Clinical Significance of Urobilin, *Arch Int Med* **28** 475 (Oct) 1921. Mueller Ztschr f klin Med **12** 45, 1887; Kong f inner Med **11** 118, 1892.

14 Schneider, J P. Anemia, *Arch Int Med* **17** 32 (Jan) 1916, Study of Bile Pigments in Pernicious Anemia, *J A M A* **74** 1759 (June 26) 1920.

15 Kahn and Barsky. Chemistry of Pernicious Anemia, *Arch Int Med* **23** 334 (March) 1919.

16 Rountree and Geraghty. *J Pharmacol & Exper Therap* **1** 597, 1909. Rountree, Fitz and Geraghty. The Effects of Experimental Chronic Passive Congestion of Renal Function, *Arch Int Med* **1** 121 (Feb) 1913.

view of our finding this condition in fourteen of fifteen cases. The protocols of twenty-five cases of pernicious anemia in which necropsy was performed at the University of Pennsylvania, showed that chronic parenchymatous nephritis was found in 36 per cent and fatty changes in 24 per cent. From these data no far-reaching conclusions may be drawn, but one can say that the most characteristic change in the kidney of pernicious anemia is parenchymatous, tubular degeneration.

The second, and probably more important, finding is the renal hemosiderosis. In the series mentioned it was noted grossly in 42 per cent of the cases. Warthin¹⁷ reports a series of eight cases of pernicious anemia carefully studied, in all of which he found renal hemosiderosis. He concludes that the iron is deposited en route to excretion. Nothnagel¹⁸ stated that the kidneys are usually pale, but often show a coffee brown color by transmitted light; he also described fatty changes and iron granules in the cells of the convoluted tubules.

Since Menglis in 1746 first found iron to be a constituent of the blood, iron metabolism and the distribution of the element has been much studied. Wells¹⁹ gives a very complete summary of the chemical changes in the blood and tissues in pernicious anemia. Erben²⁰ states that in pernicious anemia the blood proteins are decreased, both in the serum and corpuscles, but are increased per corpuscle. The proportion of water is much increased in the blood. Cholesterol is decreased in the total blood, but is increased proportionally in the corpuscles. The total iron of the blood is less than normal because of the great reduction of the number of erythroplastids, but the serum contains more than the normal amount of iron. The proportion of iron per corpuscle is also increased, as indicated by the high color index so characteristic of pernicious anemia. Erben further states that the concentration of iron in the erythroplastids is greater than the concentration of hemoglobin would warrant, and he concluded that either the hemoglobin was particularly rich in iron, or that iron was present in some other form. Rumpf²¹ confirms these analyses of Erben and adds that there is an increased sodium chloride content of the tissues, associated with a marked poverty of potassium. Fowell²² again confirmed the finding of an excess of free iron in the blood. That there is an increased elimination of iron in the urine has been shown by Kennerknecht,²³

17 Warthin Am J M Sc **124** 674, 1902

18 Nothnagel Specielle Pathologie u Therapie **7** 175, 1913

19 Wells Chemical Pathology, Ed 4, Philadelphia, W B Saunders Company, 1920

20 Erben Ztschr f klin Med **40** 266, 1900

21 Rumpf Berl klin Wchnschr **38** 477, 1901

22 Fowell Quart Jour Med **6** 179, 1913

23 Kennerknecht Virchow's Arch f Path u Physiol **205** 89, 1911

Hunter²⁴ and Finney,²⁵ but this was not confirmed by Queckenstedt²⁶ He, however, used less accurate methods

The fact that there is an excess of one of the basic products of hematopoiesis, iron, indicates that rapid hemolysis is an underlying factor Experimentally the blood picture of this disease can be reproduced by poisoning with toluylendiamin,²⁷ the toxin of *Bothriocerous cephalus*,²⁸ *p*-oxyphenylethylamin,²⁹ *Trypanosoma equiperdum*³⁰ and *Oestius equi* larvae in horses²⁸ The causative agent of pernicious anemia has never been identified It has been suggested that the disease was due to a toxin arising from unknown infection, from intestinal putrefaction, from faulty metabolism or from atrophy of the hematogenous organs³¹

Not only is there an increase in the free or inorganic iron in the blood, but much is stored in the tissues, particularly in the liver and kidneys Hunter²⁴ in a series of seven cases of pernicious anemia and seven control cases found that the iron content of these organs was as follows

	Average Per Cent of Iron		
	Liver	Kidneys	Spleen
Pernicious anemia (7)	0.270	0.090	0.125
Control (7)	0.075	0.011	0.355

The relative increase is most marked in the kidneys, Ruffel³² has obtained similar, but less striking results Squier³³ gives the following analytic figures for normal and hemolytic anemic guinea-pigs

	Liver	Kidneys	Spleen
Normal pigs	4.62	0.54	0.24
Anemic pigs (hemolysis)	25.02	3.69	2.49

These data further support the contention that there is an iron retention in hemolytic anemia Muir and Dunn³⁴ working with hemolysis in rabbits found an increase in the iron content of almost five times the normal in the liver and kidneys, but no uniform increase in the walls of the stomach or intestines Their findings are confirmed

24 Hunter Lancet **1** 283, 1903

25 Finney Brit M J, 1880

26 Queckenstedt Ztschr klin Med **79** 49, 1913

27 Syllaba Abst in Folia Hematol **1** 283 and 289, 1904

28 Seyderhelm Arch exper Path u Pharm **76** 149, 1914

29 Iwao Biochem Ztschr **59** 436, 1914

30 Krumbhaar Jour Infect Dis **22** 34, 1918, Steinfield Plasma Chlorids in Anemia, Arch Int Med **23** 511 (April) 1919

31 Bunting Bull Johns Hopkins Hosp **16** 222, 1905

32 Ruffel J Path & Bacteriol **14** 411, 1910

33 Squier J Lab & Clin Med **2** 552, 1917

34 Muir and Dunn J Path & Bacteriol **19** 417, 1914

by Boycott and Jones³⁵ Muir and Dunn³⁶ found later that if the animals were permitted to recuperate and the blood hemoglobin returned to the normal, there was no longer any evidence of iron retention in the tissues, they concluded that the iron is utilized by the bone marrow. Thus it is clear that in hemolytic anemias, as in pernicious anemia, there is a marked renal deposition of iron.

The exact location and distribution of this retained iron or siderosis is interesting. It occurs in other disorders than pernicious anemia, especially in bronze diabetes and hemochromatosis. The deposition of iron in the kidney is practically constant in its distribution. It exists as a granular deposit in the cells of the convoluted tubules, both proximal and distal. In some instances of excessive deposition it is also found in the cells of the thick limb of Henle's loop. The iron derivative of hemoglobin³⁷ has been thought of by Quincke³⁸ and Hunter³⁹ as an iron albuminate with the iron in loose combination. Gaskell and his co-workers⁴⁰ reported the siderosis confined to the convoluted tubules in the kidney in bronze diabetes. Sprunt⁴¹ found iron containing pigment in the secreting cells of all glands examined in three cases of hemochromatosis, and in the kidneys it was confined to the convoluted tubules and the lumina of the collecting tubules. Corresponding to our later experimental findings,¹ he states that some of the tubule cells are heavily laden with iron, while immediately adjacent tubules are entirely free from it. Stuhlen⁴² reports similar findings. Muir and Dunn³⁴ in their experimentally produced hemolytic anemias in rabbits found granules of hemosiderin in the cells of the convoluted tubules and a marked iron reaction there, but nowhere else in the renal tissue. Muir and M'Nee,⁴³ in studying hemoglobinuria found iron retained in the convoluted tubule cells, occurring twenty-four hours or less after hemolysis. They postulate that this may occur after hemolytic intoxication even without hemoglobinuria. In studying the increased urinary output of iron in pernicious anemia, Rous⁴⁴ found desquamated cells containing hemosiderin in fresh urine. Among his ten cases, eight showed this positive indication of renal hemosiderosis. He advocates search for such cells as a diagnostic measure.

35 Boycott and Jones Jour Path & Bacteriol **16** 347, 1913

36 Muir and Dunn J Path & Bacteriol **20** 41, 1916

37 Strasser Ziegler's Beitr z path Anat u all Path **70** 248, 1922

38 Quincke Deutsch Arch f klin Med **25** 580, 1880, **27** 193, 1881

39 Hunter Lancet, November and December, 1892

40 Gaskell, Sladden, Wallis, Vaile and Garrod Quart J Med **7** 129, 1914

41 Sprunt, T P Hemochromatosis, Arch Int Med **8** 75 (July) 1911

42 Stuhlen Deutsch Arch f klin Med **54** 248, 1895

43 Muir and M'Nee J Path & Bacteriol **16** 410, 1911

44 Rous J Exper Med **28** 645, 1918

Rous and Oliver,⁴⁵ in a histologic study of renal siderosis in rabbits, found iron only in the distal convoluted tubules and in the ascending limb of Henle's loop. These observers, as well as all the workers mentioned in the foregoing, report that there is no iron to be demonstrated in the glomerular space or in Bowman's capsule. Dubin and Pearce⁴⁶ report that in severe hemolytic anemias there is no increased iron output in the urine and feces, but their work had to do with fecal rather than urinary elimination. Warthin¹⁷ also reports eight cases of pernicious anemia, all showing renal hemosiderosis with the iron confined to the convoluted tubules.

Experimental production of renal hemosiderosis has shown¹ the same histologic distribution. The iron is usually confined to the cells of the convoluted tubules, but in some instances appears also in the cells of Henle's loops. It may be concentrated in some cells, whereas neighboring tubules may contain little or none of it. Schurig⁴⁷ found similar marked renal siderosis following daily injection of horse hemoglobin. McMaster, Rous and Larimore⁴⁸ using hemoglobin as prepared by the method of Sellards and Minot,⁴⁹ found that the renal siderosis affected primarily the proximal convoluted tubules and the ascending limb of Henle's loop, just as in pernicious anemia. But they believe that the Cushny⁵⁰ reabsorption theory of urinary secretion holds good for iron and that this iron is reabsorbed from the tubule lumen. This theory has been proved incorrect for iron.¹ In studying the renal elimination of bilirubin, Haesler, Rous and Brown⁵¹ found that the pigment accumulates, as does hemosiderin, in the convoluted tubules and Henle's loop, but the glomeruli are unstained. This is confirmed by Quincke's previous observations.⁵² In coexistent renal disease, bilirubin may not come through, but be stored in the renal cells (Nonnenbruch⁵³). Fukuda and Oliver,⁵⁴ in studying the excretion of hemoglobin by the kidney in animals, believed that at least some of the pigment was secreted by the cells of the convoluted tubules, and that all of it did not pass through, but was retained.

The uniformity of these pathologic and experimental reports is striking. The convoluted tubule cells are almost universally conceded as being the site of secretion and deposition of iron containing pigments, or simple iron salts. To the foregoing data can be added a

45 Rous and Oliver J Exper Med **28** 629, 1918

46 Dubin and Pearce J Exper Med **25** 675, 1917, Ibid **27** 479, 1918

47 Schurig Arch Exper Path u Pharm **41** 29, 1898

48 McMaster, Rous and Larimore J Exper Med **35** 521, 1922

49 Sellards and Minot J M Res **37** 161, 1918

50 Cushny The Secretion of Urine, Monographs of Physiology, 1917

51 Haesler, Rous and Brown J Exper Med **35** 533, 1922

52 Quincke Nothangel's Specielle Path u Therap **18** 83, 1899

53 Nonnenbruch Mitt Grenzgeb Med u Chir **21** 470, 1919

54 Fukuda and Oliver J Exper Med **37** 83, 1923

report of fifteen⁵⁵ cases of pernicious anemia in which the kidneys were studied by the direct Prussian blue reaction for iron,¹ rather than by the method of Nishemura,⁵⁵ which is more complex and no more satisfactory.

In fourteen of the fifteen cases, a deposition of iron in the cells of the convoluted tubules was demonstrable. Of these cases, seven, or about one-half, showed only a small amount, the other, a great deal. The iron reaction was always sharply localized, never diffuse and showed iron present only in the cell membrane of the convoluted tubules or in the débris in the lumina. No iron was detected in the glomerular spaces or capsule. The cases showing the largest amount of iron in the tubules had a lower hemoglobin reading at the time of death than the others. The average hemoglobin content of the blood in three cases with only a little iron retained was 45 per cent, the average hemoglobin for five cases with marked deposition of iron was 17 per cent.

Having established that in pernicious anemia there is a marked deposition of iron in the cells of the convoluted tubules, the next problem is: What effect has this iron on renal function? The fact that the renal disorder is usually worse when the anemia is most marked may be explained in two ways either the anemia is the direct cause of the renal disturbance, or at that time the renal siderosis is most marked and therefore the effect of the iron most conspicuous.

Sellards and Minot⁵⁶ found that considerably less hemoglobin is required for injection to produce hemoglobinuria in persons with pernicious anemia than in normal persons. In secondary anemia or in any case in which there is no excessive destruction of blood the renal threshold for hemoglobin is about normal. They found further, that the hemoglobin tolerance bore no relationship to the red corpuscle count, but varied inversely with the amount of blood destruction taking place at the time. This finding is interesting in connection with the deposition of iron (which also depends on the amount of blood destruction going on) for the cells are already loaded with iron compounds and therefore cannot retain the excess as would normal cells which are practically free of ionizable iron. The lowered threshold therefore may be largely explained by the renal siderosis.

It was thought that an experimental study of the renal function in anemias with and without renal hemosiderosis and in hemosiderosis

⁵⁵ The material from these fifteen cases was collected through the courtesy of Dr E B Krumbhaar, Philadelphia General Hospital, Dr H Oberhelman, Presbyterian Hospital Chicago, Dr H G Wells, University of Chicago, and Dr L Stieglitz, New York. I take this opportunity of expressing my appreciation of their kind cooperation.

55 Nishemura Centralbl f allg Path u Path Anat 21 10, 1910

56 Sellards and Minot J M Res 34 469 1916

without anemia might throw further light on the point of view that the iron deposition in the kidney is largely responsible for the renal damage in pernicious anemia. The tabulated protocols of such experiments follow.⁵⁷

PROTOCOLS OF EXPERIMENTS

EXPER 1—*Simple Secondary Anemia*—Dog, male, weight, 15 kilograms

Nov 15, 1922 Healthy dog, hemoglobin, 95 per cent (Dare)⁵⁷ Urine No albumin or casts, acid, specific gravity 1.032 Intravenous "phthalein" excreted 90 per cent, overnight

Nov 16, 1922 Bled 300 cc, hemoglobin after bleeding, 80 per cent

Nov 20, 1922 Bled 300 cc, hemoglobin after bleeding, 70 per cent

Nov 23, 1922 Bled 200 cc, hemoglobin after bleeding, 65 per cent

Nov 26, 1922 Bled 200 cc, hemoglobin after bleeding, 50 per cent Urine

No albumin or casts, acid, specific gravity 1.030

Dec 3, 1922 Bled 300 cc, hemoglobin after bleeding, 40 per cent

Dec 6, 1922 Bled 200 cc, hemoglobin after bleeding, 35 per cent

Dec 10, 1922 Bled 150 cc, hemoglobin after bleeding, 30 per cent Later in day hemoglobin, 35 per cent "Phthalein," overnight, 82 per cent Urine No albumin or casts

Dec 15, 1922 Hemoglobin, 40 per cent "Phthalein" overnight, 86 per cent

Urine No casts or albumin

EXPER 2—*Simple secondary anemia*—Dog, male, weight, 10 kilograms

Nov 17, 1922 Hemoglobin, 93 per cent "Phthalein" overnight, 88 per cent Urine No albumin or casts, acid, specific gravity 1.029

Nov 18, 1922 Bled 300 cc, hemoglobin after bleeding, 85 per cent

Nov 20, 1922 Bled 200 cc, hemoglobin after bleeding, 78 per cent

Nov 23, 1922 Bled 150 cc, hemoglobin after bleeding, 72 per cent

Nov 26, 1922 Bled 200 cc, hemoglobin after bleeding, 65 per cent Urine no albumin or casts

Nov 28, 1922 Bled 200 cc, hemoglobin after bleeding, 55 per cent

Nov 29, 1922 Bled 150 cc, hemoglobin after bleeding, 50 per cent Urine no albumin or casts, clear, acid, specific gravity 1.024

Dec 4, 1922 Bled 150 cc, hemoglobin after bleeding, 47 per cent

Dec 8, 1922 Bled 200 cc hemoglobin after bleeding, 40 per cent Urine no albumin or casts, clear acid "Phthalein," overnight, 80 per cent

Dec 12, 1922 Bled 200 cc, hemoglobin after bleeding, 32 per cent Urine still perfectly normal

The animal was not killed, but allowed to recover and used later for other work

The results of these two experiments indicate that simple secondary anemia alone does not cause any conspicuous change in renal function or kidney damage as manifested by albumin and casts

EXPER 3—*Secondary Anemia with Reinfusion of Hemoglobin*—Dog, female weight, 12 kilograms

Dec 10, 1922 Hemoglobin, 92 per cent, "phthalein" overnight, 90 per cent Urine no albumin or casts, clear, acid, specific gravity 1.028 Bled 300 cc,

57 The Dare instrument was used throughout for hemoglobin estimations. The phenolsulphonephthalein test was carried out by injecting 1 cc of the ampule solution of the dye intravenously in the evening and collecting all the urine the next morning from the metabolism cage. This was then titrated against a standard in the usual way.

hemoglobin after bleeding, 80 per cent The blood centrifuged, corpuscles separated, washed and then hemolyzed with distilled water, 50 cc of this were reinjected intravenously

Dec 11, 1922 Hemoglobinuria

Dec 13, 1922 Bled 200 cc, hemoglobin after bleeding, 78 per cent Corpuscles treated as above, and 40 cc of hemoglobin solution injected intravenously Hemoglobinuria followed promptly

Dec 14, 1922 Hemoglobinuria, no casts or albumin detected

Dec 15, 1922 Urine clear, no casts or albumin

Dec 16, 1922 Bled 400 cc, hemoglobin after bleeding, 60 per cent 400 cc of hemoglobin solution reinjected as above

Dec 18, 1922 Bled 300 cc, hemoglobin after bleeding, 51 per cent, 35 cc of hemoglobin solution reinjected as above Hemoglobinuria

Dec 20, 1922 Bled 250 cc, hemoglobin after bleeding, 40 per cent Hemoglobin solution reinjected as above

Dec 21, 1922 Urine Clear, both albumin and casts present and a trace of hemoglobin, specific gravity, 1.018

Dec 22, 1922 Urine Clear, albumin and casts both present, no hemoglobin, specific gravity, 1.016, acid Bled 300 cc, hemoglobin after bleeding, 28 per cent

Jan 10, 1923 Urine Clear, dark straw, albumin and casts both present, acid, specific gravity, 1.024 Bled 300 cc, hemoglobin after bleeding, 34 per cent Hemoglobin reinjected as above Hemoglobinuria occurred as before, but there was less in the urine than previously

Jan 13, 1923 "Phthalein" overnight, 60 per cent

Jan 15, 1923 Hemoglobin, 40 per cent Urine Albumin and casts both present, especially the former No hemoglobinuria, specific gravity, 1.014

The above experiment, on the other hand, indicates that an anemia with hemoglobinemia and therefore renal hemosiderosis leads to distinct renal damage as evidenced by the fall in the phenolsulphonephthalein excretion from 90 to 60 per cent and the appearance of albuminuria and casts

EXPER 4—Experimental Hemosiderosis Without Anemia—Dog, terrier, female, weight, 7,680 gm

Jan 12, 1923 "Phthalein" overnight, 90 per cent Urine Clear, dark amber, no albumin or casts, or sugar Specific gravity, 1.05

Jan 13, 1923 Injection of 1 gm of green ferric ammonium citrate partly intravenously, partly subcutaneously, marked amount of iron in urine after the injection

Jan 16, 1923 Injection of 0.75 gm green ferric ammonium citrate intravenously Afterward there was a great deal of iron in the urine "Phthalein" overnight, 65 per cent Urine A few hyaline casts (some with iron in them), and some albumin, specific gravity, 1.02, acid

This experiment unfortunately was discontinued because of an illness of the author

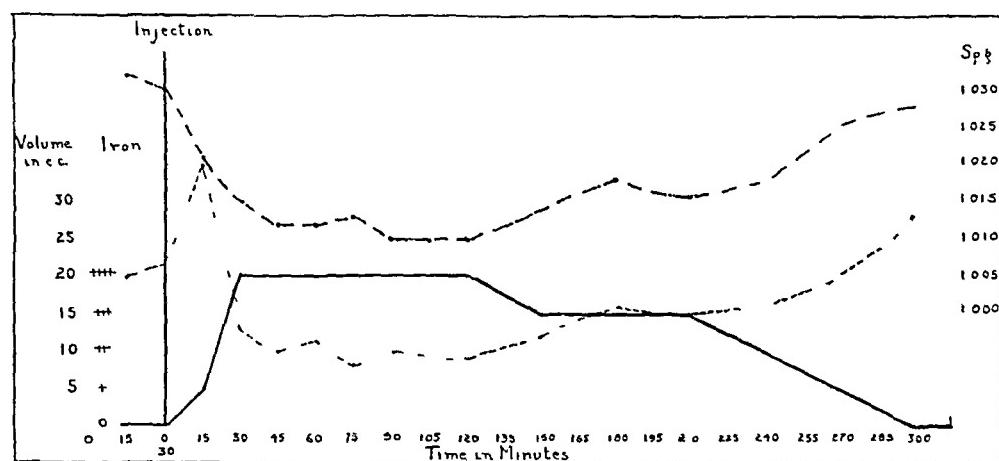
It has been shown in rabbits¹ that iron is secreted by the convoluted tubules, and that in the process of this secretion it causes distinct functional changes The foregoing experiment partly confirms this finding in a dog During the period of elimination of iron following intravenous injection of iron salts, there is a brief and transient

diuresis, followed by an antidiuresis. Furthermore, in rabbits, during iron elimination by the kidneys the specific gravity of the urine is lowered, and thus not only the volume of the urine, but the total solids are reduced by the action of the iron.

The following experiment shows that the same results may be obtained in a dog.

EXPERIMENT 5—Dog, female, weight, 8 kilograms. The animal was tied to the table, catheterized without anesthesia, and the urine collected, the catheter being left in place and new specimens obtained every fifteen minutes. After two preliminary control readings, 0.8 gm of green ferric ammonium citrate were injected into the jugular vein with no apparent toxic reaction. The results are shown graphically in the chart.

The foregoing experiment reproduces the results previously obtained with rabbits and shows that iron has a decided effect on renal function.



Results in Experiment 5. The continuous line indicates the iron in the urine, the broken line, volume of urine per unit of 15 minutes in cubic centimeters, dot and dash line, specific gravity of urine.

during the time of its elimination. Iron, during its elimination by the kidneys, causes a fall in the rate of water excretion and a fall in the specific gravity, indicating a marked diminution of all secretion at that time.

COMMENT

That iron is retained in the convoluted tubule cells in pernicious anemia has been demonstrated. It has also been shown that there is an increased secretion of iron salts in the urine. Iron retained in the tubular epithelium in rabbits may gradually cause a mild nephritis, or disturbance of renal function, as indicated by the appearance of albuminuria and casts, and in some instances ascites. Trivalent iron, according to Fischer,⁵⁸ is the most active of all cations in preventing

the hydration of colloids, or in freeing water from them. It should therefore be an active diuretic. It is diuretic in the initial phases of the experiment, while there are free iron ions in the tissues and circulation, but as soon as it accumulates in the secreting cells the reaction would be reversed, as is the case. The presence of iron in the cells in abnormal quantity prevents their taking up water and therefore the resulting antidiuresis. The fall in the specific gravity of the urine is likewise dependent on this phenomenon, as the solutes cannot pass if their solvent, water, is blocked. This all points to a secretory function for the convoluted tubules, which in pernicious anemia is interfered with by the accumulation of iron in the cells of the convoluted tubules.

The effect of iron on the urine volume and specific gravity is particularly interesting in view of the clinical observation on renal function in pernicious anemia, in which the ability of the kidney to concentrate the urine is most characteristically affected. The relation between these two phenomena, clinical and experimental, seems more than coincidental, and it may be concluded that this correlation of findings is of significance in connection with the etiology of the nephritis, or renal damage of pernicious anemia.

The intracellular activities of iron are not all injurious, however. Bayliss⁵⁹ emphasized the important function of iron compounds as vehicles for oxygen, to be consumed elsewhere. This is also pointed out by Peters⁶⁰. However, the iron so utilized is not electrolytic, inorganic iron. Ferric compounds do not carry oxygen, but are catalytic in stimulating the tissues to consume oxygen.⁶¹ Thurnburg⁶² observed that lecithin consumed oxygen in the presence of iron salts, but not without them. Therefore ionized iron has a powerful chemical catalytic action in stimulating oxidation as well as the physical action discussed in connection with colloid hydration and diuresis.

The therapeutic use of iron in pernicious anemia is a common method of treatment, used formerly more than it is now. Recent work has shown that iron is of little value in the treatment of this disease. This conforms with the knowledge that there is a superabundance of this element already in the tissues. Musser⁶³ showed that inorganic iron did not increase the speed of blood regeneration in dogs rendered

59 Bayliss Principles of General Physiology, New York, Longmans, Green & Co, 1915, (pp 592 and 614)

60 Peters Jour Physiol **44** 131, 1912

61 Warburg Ergeb Physiol **14** 253, 1914

62 Thurnburg Skand Arch Physiol **24** 90, 1911

63 Musser Influence of Inorganic Iron on Regeneration of Blood After Hemorrhagic Anemia, Arch Int Med **28** 638 (Nov) 1921

secondarily anemic Whipple and Robscheit⁶⁴ obtained similar results, and Whipple⁶⁵ found that arsenic and iron were inert in this connection. Weber⁶⁶ and Ashby⁶⁷ come to the same conclusion, the latter even questioning whether there is an increased hemolysis. Whipple⁶⁴ concludes that the deficiency is in the stroma material necessary for the manufacture of erythroplastids rather than in the hemoglobin factor.

SUMMARY

It has been shown that

- 1 Disturbances of renal function are common in pernicious anemia
- 2 Histologic examination of the kidneys frequently discloses degeneration of the tubular epithelium
- 3 There is a deposition of iron in the convoluted tubules of the kidney
- 4 Iron in such a location probably causes damage to the epithelium
- 5 Iron in these cells inhibits the passage of water and total solids, and reduces the specific gravity of the urine
- 6 Fixation of the specific gravity and an increase of the night over the day urine volume is characteristic of the alteration of renal function in pernicious anemia

The correlation of these findings leads to the conclusion that the renal functional changes in pernicious anemia may be attributed at least in part to the accumulation of iron in the convoluted tubules, rather than to the anemia alone. The hemosiderosis and the resulting changes in function are so specific that one may speak of this condition as the nephritis of pernicious anemia. It is particularly interesting in view of the fact that the changes are apparently purely tubular and result from a perverted metabolism.

⁶⁴ Whipple and Robscheit Iron and Arsenic as Influencing Blood Regeneration Following Simple Anemia, *Arch Int Med* **27** 291 (May) 1921

⁶⁵ Whipple Pigment Metabolism and Regeneration of Hemoglobin in the Body, *Arch Int Med* **29** 711 (June) 1922

⁶⁶ Weber Ztschr f Biol **70** 168, 1920

⁶⁷ Ashby J Exper Med **34** 127, 1921

PARALYSIS OF THE LEFT RECURRENT LARYNGEAL NERVE IN MITRAL STENOSIS

REPORT OF A CASE, AND A REVIEW OF THE LITERATURE*

M NOTKIN, MD

MONTREAL, CANADA

During the past twenty-five years a rather uncommon complication of mitral stenosis, paralysis of the left recurrent laryngeal nerve, has caused considerable interest. The chief importance of the condition lies, perhaps, in the diagnosis, more especially in its distinction from aortic aneurysm, but in addition there has been a great deal of controversy and discussion as to the method of production of the paralysis and its course and termination. Since O'Brien first described the condition (1897), four different theories and many modifications have been proposed as to its mechanism, and each has for its support not only the opinion of various clinical investigators, but also the findings in a number of necropsies. Seventy-four cases have been reported, in seventeen of which necropsy was performed.

It is my purpose to report a case diagnosed, treated and examined postmortem in the Montreal General Hospital, to review the literature, to discuss the diagnosis, the method of production of the paralysis, the treatment and prognosis.

REPORT OF A CASE

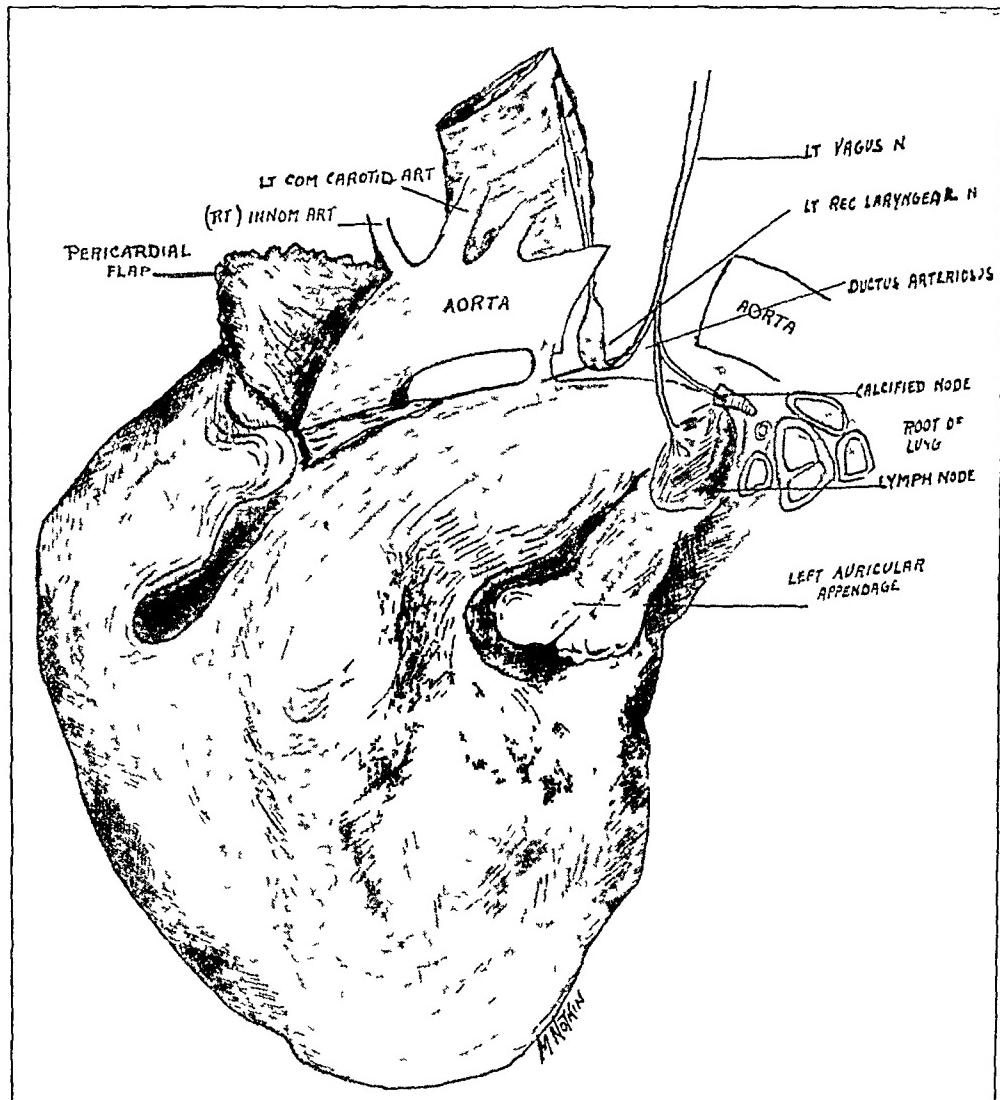
M G H, a man, aged 31, in the service of Dr F G Finley, complained of dyspnea, weakness and swelling of the legs and abdomen. For the past three and a half years he had been troubled with dyspnea, palpitation of the heart and edema, on account of which he had to stop work for several months at a time. On March 1, 1921, he was admitted to the Montreal General Hospital and was discharged in one month, improved. Three weeks later he was readmitted with the same symptoms. He assumed the orthopneic position. A systolic impulse in the veins extended up each side of the neck as far as the ears. There was edema of the lower extremities and scrotum. The abdomen showed dilated superficial veins. The liver was slightly enlarged. The fundi were normal. The pulse was irregular in volume and rhythm. The blood pressure was systolic, 118, diastolic, 82. There was some bulging of the precordium. The apex beat was diffuse in the left fifth and sixth spaces. The maximum impulse was 11 cm to the left of the midsternal line. The upper limit of dulness was at the second costal cartilage and the right border 5 cm from the midsternal line. At the apex there was a blowing systolic murmur propagated toward the axilla and along the sternum. The second sound was followed by a faint murmur. At the base the second pulmonary sound was accentuated (Dr F G Finley).

Roentgen-Ray Report (Dr Wilkins)—Roentgen-ray examination of the chest showed marked increase in the transverse diameter of the heart at the apex.

*From the service of Dr F G Finley and the pathological laboratories of the Montreal General Hospital.

both to the right and to the left. No abnormality was noted as being associated with the aortic shadow, and the upper portion of the posterior mediastinum was clear.

Course of Disease—The abdomen was tapped every two or three weeks, and between 6,000 and 8,000 c.c. of turbid, straw-colored fluid were withdrawn each time. Infarcts of the lung developed. Six days before death hoarseness appeared and remained until death. A laryngoscopic examination by Dr R P Wright revealed almost complete limitation of movement of the left cord,



Semidiagrammatic drawing of heart as found in author's case. Aorta, pulmonary artery and lymph node are shown to be drawn apart. A section of the aorta is shown to be removed, exposing the left vagus nerve as it hooks around the aorta.

marked thickening and some interarytenoidal bogginess. The right cord moved freely and was greatly thickened and slightly reddened.

Anatomic Findings—The body was well developed but emaciated. The conjunctivae were jaundiced. The skin was dry and scaly, the abdomen distended and the superficial veins dilated. There was chronic passive congestion.

of the lungs, liver, spleen, kidneys and mesenteric veins. There were multiple infarcts of the lung, fibrous pleural adhesions on the left side, cirrhosis of the liver (slight), ascites, edema (slight) and jaundice.

The heart was large, the myocardium firm and brownish. The left auricle, right auricle and right ventricle were all markedly dilated and hypertrophied, while the walls of the left ventricle were not noticeably thickened.

The cusps of the mitral valve were fused and calcified, leaving an orifice measuring 17 cm by 0.8 cm. The tricuspid valve was normal except for the anterior cusp, which was slightly thickened at the free edge. The left anterior and the posterior cusps of the aortic valve were considerably thickened about the nodule of each cusp. The pulmonary valve was free.

The pulmonary artery was considerably dilated (3.75 cm at its widest diameter), and in the angle between the pulmonary artery, aorta and ductus arteriosus (nonpatent) was lodged a lymph gland (1.5 cm by 1.25 cm), lending itself in this position as additional means of transmitting pressure upon the aorta and directly upon the recurrent laryngeal nerve.

The left recurrent laryngeal nerve as it hooked under the aorta showed marked flattening and was pale gray. The remainder of the left vagus divided into two main branches. One branch ran through the connective tissue at the base of the lymph gland mentioned above (to form the anterior pulmonary plexus), and another ran toward the posterior aspect of the root of the lung. On its course this branch was held fast in a calcified lymph node lying a little in front of and below the aorta. It was difficult to determine whether or not during life this calcified mass exerted pressure upon the aorta and indirectly upon the left recurrent laryngeal nerve.

The trachea was somewhat flattened on the left side, at that area which is in contact with the arch of the aorta.

REVIEW OF THE LITERATURE

Theories of the Production of the Paralysis of the Vocal Cord —

1 Ortner, whose two cases came to necropsy, believed that the enlarged left auricle pressed the left recurrent laryngeal nerve against the aorta producing a pressure paralysis.

2 Klaus, in 1900, reported a case which at necropsy showed, besides a dilated left auricle, a greatly hypertrophied right ventricle which had forced the heart into a transverse position. He believed that the enlarged right ventricle had rotated on the diaphragm in such a way as to shift the base of the heart to a lower position, dragging with it the ductus arteriosus, which in turn pulled on the aorta with resultant traction on the left recurrent laryngeal nerve.

3 Von Schroetter described a case in which the mechanism was altogether different. There was a patent ductus arteriosus as large as the greatly dilated pulmonary artery, which pressed the laryngeal nerve against the aorta at the point of origin of the ductus.

4 Alexande's case, in 1904, without necropsy, showed on roentgenographic examination a dilated left auricle and pulmonary artery. In view of the normal anatomic relations of the left auricle, pulmonary artery, laryngeal nerve and aorta, he suggested that the paralysis was due to pressure of the pulmonary artery upon the nerve. Such a condition was actually found at necropsy by Fischauer (1905).

5 Other reports followed with discussions and additions, including the statement that the laryngeal nerve may be involved in the cicatricial tissue following pericarditis, mediastinitis and other lesions that may be associated with mitral stenosis

COMMENT

Oitner's theory was supported by necropsy findings by Herrick, Hofbauer (Case 2), Ceraulo, Oslei (Cases 1 and 3), Guder and Dufour (Case 2) and Bonardi, as well as the opinions of Sheldon, Thorne, Harris, Boinet, Palasse, Gouget, Perotta, Cohn and Sforza, based on observations on cases in which postmortem examinations had not been made. Some of them accepted Oitner's theory in cases in which there was cardiac decompensation and that of Kraus in cases in which compensation had produced an hypertrophied right ventricle.

Kraus, Dmitrenko and others take exception to Oitner's view on the ground that the left ventricle is separated from the left recurrent laryngeal nerve by the pulmonary artery, and therefore cannot itself press upon it. They point out that there are many cases of extreme dilatation of the left auricle from other causes than mitral stenosis, but in such cases paralysis of the left recurrent laryngeal nerve is unknown.

Fetterolf and Norris by cross sections and dissections of formaldehyd hardened thoraces have shown the position of the left auricle to be such that

In expansion, the auricular appendix would probably be the first part affected as it lies free and unadherent to anything. Should it be dilated it would press upward and backward, thrusting the left pulmonary artery against the aorta, the left pulmonary vein against the pulmonary artery and forcing the distal portion of the latter against the aorta. Later when the atrium or main cavity dilated the proximal part of the pulmonary artery is jammed upward and backward, mainly by the root of the left pulmonary vein. The nerve is thus squeezed between the pulmonary artery on the one hand and the aortic arch or ligamentum arteriosum on the other.

This report, antagonistic to Ortner's and Kraus' theories, strengthens the view of Alexander and Frischauer, which has for its support the necropsy reports of Frischauer, Mead, Garland and White and our own case, and the views of Dmitrenko, Lian and Marcolles, Carrau, Guttman and Neuhoff and also Gillies, who described in a case without mitral stenosis a paralysis of the recurrent nerve due to pressure of a dilated pulmonary artery.

Lian and Marcolles claim that additional etiologic factors are necessary. They suggest that there should be something of sufficient hardness to compress the nerve, and propose either the presence of old thrombotic masses in the left auricle or a certain degree of chronic mediastinitis.

Kraus, who had the support of Hofbauer, Quadione and others, states that at necropsy in his case the ductus arteriosus was found to lie in a horizontal position and therefore must have been pulled down by the rotated heart. Fetterhoff and Norris have shown that this horizontal position of the ductus is the normal one, and state that even if in Kraus' case its position was more nearly horizontal than usual it was probably caused by a pushing up of the pulmonary artery. Moreover, it is hardly likely that the ductus, a structure of about 2 mm in diameter, would produce the descent of a large structure like the aorta, supported and held in position as it is by the great vessels which arise from it, as well as the deep cervical fascia and other structures.

Von Schroetter's findings of incarceration of the nerve by the patent ductus and aorta have also been reported by Zimbler and Mead. Gerhardt affirmed the possibility of paralysis of the recurrent nerve due to this cause.

It appears, therefore, that if any one mechanism is adopted to explain the production of the paralysis, preference must be given to that in which the pressure of the pulmonary artery upon the nerve (whether due to enlargement of the artery or to its displacement) is the major factor. Here it is not necessary to strain the imagination since the anatomic position of the parts is such that on enlargement of the heart the pulmonary artery must come in contact with the nerve. Moreover, hypertrophy and dilatation of the pulmonary artery occurs in most of the reported cases.

PARALYSIS OF THE LEFT RECURRENT LARYNGEAL NERVE

Paralysis of this nerve produces a change in the character of the voice varying from a low pitch to aphonia, depending on the extent to which the nerve is affected. The onset may vary both in the stage of the cardiac disease at which it occurs and in the rapidity of onset.

Stage of Disease at Which Paralysis Occurs—The reported cases may be divided into four groups (1) those in which paralysis occurs while compensation is still good—eight cases, (2) those in which compensation is fair as evidenced by dyspnea, etc., but no edema—seventeen cases, (3) cases in which compensation is broken—twenty-three cases, (4) cases in the agonal stage in which paralysis occurs a few days before death—four cases. Most cases occur when there is a disturbance of compensation with consequent dilatation of the heart. Sometimes, however, as in the cases of Hofbauer (Case 1), Thorne, Alexander, Davis, and Hall, the patient primarily comes to seek the advice of the laryngologist for hoarseness, and the cardiac condition is found in the subsequent examination.

Analysis of the Reported Cases

Reporter	Patient Age	Sex	Heart Lesion	Brief History	Pulses	Pulsation at 2d Cartilage	Recurrent Paroxysms	Change of Voice on Position	Roentgen Rx	Necropsy	Remarks
Ortner	17	M	Double mitral and tricuspid stenosis obliterating pericarditis	Venous pulse in neck, dyspnea and orthopnea, edem, icterus	Left carotid smaller than right		0	Reappears from time to time	Auricle compressed against left bronchus, pericarditis, pulmonary artery dilated	Nerve degenerated auricle filled with thrombus right pulmonary artery	Nerve flattened and discolored right vein dilated
Herrick	31	F	Double mitral and aortic trikuspid stenosis, adherent pericarditis	Rheumatic arthritis for 12 years, last 2 years short breath, weak on exertion lately edema and hoarseness, large liver, anasarca and edema, hoarseness 1/2 year ago (6 months after patient had pleurisy and pericarditis)					Nerve embedded in cervical tissue and compressed between torta and auricle which forced its way between torta and pulmonary artery considerably distorting normal anatomic relations, nerve microscopically degenerated	Compression probably due to (1) Cervical contraction (2) auricular pressure	
Kraus	38	M	Mitral stenosis obliterative pericarditis and pleuritis						Right ventricle so large that it heart is rotated pulling on pulmonary artery, aortic ligament and torta and resulting in traction on nerve, nerve gray and degenerated	Pulmonary artery dilated, nerve discolored, on phonation tremulous movement of left arytenoid cartilage	
Von Schroetter	21	F	Double mitral, tricuspid insufficiency, aortic stenosis (slight)	Heart disease since 1 year, no decompensation mentioned	Rapid, irregular	1st and 2d		'In reverse position of the ut'	Nerve compressed between origin of ductus arteriosus and torta, constricted and discolored, pulmonary artery larger than ascending aorta, its branches larger than normal, ductus arteriosus as large as pulmonary artery	None	
Hofbauer	15	F	Double mitral, tricuspid insufficiency, patent ductus arteriosus	Faint syndrome since childhood, cyanosed since birth, congestion of abdominal organs edema				At upper left border there is curve at 2d cartilage which is not dull to percussion			
Syllab Sheldon	32	M	Mitral stenosis					Two pulsations shadows at left border of heart due to left auricle and pulmonary artery	None		
	47	M	Mitral stenosis						Improved with heart condition	Both cords worked normally on discharge	

Quidrone	1	F	Mitral stenosis and insufficiency	Bilateral paresis	Nerve normal	No notes	No notes	
	2	F	Mitral stenosis	Bilateral paresis				
	3	F	Double mitral lesion	Bilateral paresis				
	4	M	Double mitral lesion	Bilateral paresis				
	5	M	Double mitral lesion	Bilateral paresis				
	6	F	Mitral stenosis	Bilateral paresis				
	7	F	Mitral stenosis	Bilateral paresis				
Harris	15	F	Mitral stenosis	At 24, dyspnea at 27, became worse and lost voice, venous pulse present in neck	Small, rapid			
	8	M	Double mitral lesion					
Alexander	20	F	Mitral stenosis	Subject to cardiac attacks of rheumatic origin, last one 2 years ago, since then effort dyspnea, hoarse for 8 weeks only, but later recurred and remained, for which she sought medical advice, slight dyspnea, no cyanosis	Hoarse 8 weeks, normal 6 weeks	Same as Hoffbauer		
Frischhauer						Same as Hoffbauer		
Cavello	30	F	Double mitral, tricuspid insufficiency	Equal, small				
Hoffbauer		M	Mitral stenosis	Heart disease since 2 years with hoarseness skin livid, before this in good health				
Pal Tretrop	19	M	Mitral insufficiency			Paralysis appeared and disappeared patient got worse or better		
I'horne	17	I	Mitral stenosis		Equal	Enlargement to left, pulsatile curve on left side	None	
Howard	10	F	Double mitral tri cuspid insufficiency pericarditis			Normal compressed between left auricle and pulmonary artery, auricle dilated		

Analysis of the Reported Cases—(Continued)

			Dilated auricle pressing on nerve		
2	24	M	Double mitral lesion		
3	42	F	Mitral stenosis, tortortis and aortic insufficiency		
Osler	1	45	F	Mitral stenosis	
	2	27	F	Double mitral stenosis	
Palasse	3	46	M	Double mitral aortic insufficiency	
	20	F	Mitral stenosis and insufficiency		
Perotta Boinet	1	28	F	Mitral stenosis, tricuspid lesion	
	25	F	Mitral stenosis		
Cohn	2	23	F	Mitral stenosis	
	31	F	Double mitral lesion		
Dmitrenko			Mitral stenosis		
	29	M	Mitral stenosis		
Mend			Mitral stenosis, aortic stenosis, patent ductus arteriosus, sclerosis of aorta		
	26	F	Mitral stenosis, aortic stenosis, patent ductus arteriosus, sclerosis of aorta		
					Aortitis and periaortitis probable cause of prosthesis, no further report. No decompensation when paraparesis occurred, patient improved with treatment, died 1 year later
					Dilated heart, dilated torta without sac Dilated auricle
					None
					None
					None
					Nerve compressed between dilated auricle and torta right ventricle extremely dilated, nerve sclerosed, white and opaque
					None
					Dilated auricle, no aneurysm
					Greatly enlarged heart, especially left auricle, shadow triangular, few enlarged glands
					Dilation of left auricle which author assumes presses on nerve
					None
					None
					Dilation of left auricle root of torta displaced to the right.
					None
					Several recurrences
					3d and 4th
					Irregular pulse
					Irregular pulse
					Equally rate Q8, blood pressure, right 125, left 115
					Pulse at 2d car tibia easily seen
					Congenital heart disease, subject to bronchitis, paroxysms improved then recurred with broken composition
					Dilated heart, left auricle and right ventricle extremely large, pulmonary artery dilated and larger than aorta, patent ductus arteriosus, retro microscopically to be not degenerated

Analysis of the Reported Cases—(Continued)

Reporter	Patient Age	Sex	Heart Lesion	Brief History	Pulses	Pulsation at 2d Cervilage	Recurrent Paralysis	Change of Voice on Position	Roentgen Ray	Necropsy	Remarks
Mosby and Portocollis Peteroff and Norris (Dr T H Klier)	29	M	Mitral stenosis and insufficiency	Onset of hoarseness without symptoms of heart trouble, sometimes relieved by belching, later with onset of cardiac symptoms, voice more hoarse with cough when in recumbent position, edema, dyspnoe, dulness above heart and to the left of sternum	Left radial pulse smaller than right				Heart enlarged to the left, bronchial lymph glands enlarged	None	Details not available
Vaquez and Bordet Chaisse, Thibaut and Gillard	22	F	Mitral stenosis	Onset of heart disease 2 years ago, 1 year ago voice changed and grew progressively worse, dyspnoe, palpitation, cough 10 years ago heart disease following scarlet fever, for the last 2 years had recurrent attacks of breaking compensation, "and one morning during a cardiac attack "woke with voice "broken", this lasted 10 days and became normal followed by recurrences preceded by cardiac symptoms, last one remained 3 weeks (until death) edema, cyanosis, enlarged liver	Regular, equal			No change	Dilated left auricle, no enlarged glands	None	After eleven months' treatment, no improvement in heart or vocal condition
	28	F	Mitral stenosis	Heart disease of rheumatic origin				No change	Dilated left auricle, no enlarged glands	None	Dilated left auricle, fibrous tissue causing strong adhesion between left auricle, aorta, esophagus and left bronchias, left auricle filled with clots, right ventricle large
De Haviland Hall	19	F	Mitral stenosis	Right radial pulse larger than left, small, regular				No change	Dilated heart	None	Dilated auricle, dilated and pulsating pulmonary artery, degree of mediastinitis, particularly in neighborhood of pulmonary artery
Lian and Mcrobes	42	F	Mitral stenosis	Heart disease of rheumatic origin for 20 years, the last 2 years had two cardiac crises with right hemiplegia, 5 months after last attack began to get hoarse at certain moments, in few months voice improved, but this was due to accommodation of right cord				Improved with improvement of heart condition		Right pupil larger than the left	Partial paralysis of left vocal cord
Permewan 1 (Dr N Raw)			Mitral stenosis								Brief verbal report

							Brief verbal report
Guttmann and Neuhoff	1	25	F	Patent foramen ovale Mitral stenosis	Heart disease of rheumatic origin since 3 years, hoarseness 3 months ago, dry pericarditis, 3 weeks later evidence of fresh pericarditis over pulmonary veins, dyspnea and palpitation but no edema	Dilated left auricle and pulmonary artery, aorta somewhat dilated	Enormously dilated heart Patient died in a few weeks
Rosenthal	1	4½	F	Mitral stenosis, aortic stenosis	Six weeks after onset of rheumatic (?) fever, dyspnea, etc., 2 weeks after fever, hoarseness, dyspnea, cyanosis, palpitations, for past 4 years difficulty in breathing, during the last year severe cardiac atacks, and lately dyspnea, cough, palpitations and edema, hoarseness developed while in hospital	Heart markedly enlarged	None
	27	M	M	Mitral stenosis and insufficiency	Four years ago onset of cardiac disease of rheumatic origin, decompen-sation 2 years ago, improved, well until 1 year later when, while walking, suddenly lost voice	Right and left sided cardiac dilatation	None
Cartau		16	F	Mitral stenosis		Dilated auricle and right ventricle, some tracheobronchial glands	None
Frestolt and Strain/ S. Gillies Davis	1	10	F	Mitral stenosis	Five years ago lost voice which became normal after 2 months, 2 years ago bronchitis with loss of voice, since then no change in voice	Voice better when patient is standing up than when lying down	Heart dilated and displaced to the left, opaque posterior mediastinum
	2	19	M	Mitral insufficiency, acute endocarditis and pericarditis	One year ago heart trouble, voice weak and hoarse, 6 months later convalescent but paroxysms complete	After 3 years	No details given
Shuster Garland and White	1	27	M	Mitral stenosis	Athletic until 2 years ago, rheumatic heart disease 6 months ago, caught cold and became hoarse, hoarseness persisted with remissions, it same time dyspnea on exertion compelled him to stop work 17 weeks ago, cyanosis	Equal, synchronous regular	Details not available Patient living, more or less complete paroxysms of left cord
						Remissions reported	Patient improved compensation by right cord
						Dilated left auricle, peribronchial thickening with enlarged bronchial glands	Details not available Right pupil larger than left, discharging under observation two years, improved, but hoarseness persists

Analysis of the Reported Cases—(Continued)

Reporter	Patient	Heart Lesion	Brief History	Pulses	Change of Voice on Position	Roentgen Ray	Necropsy	Remarks
	Age	Sex						
2	53	F	Mitral stenosis	Heart disease since 6 years, worse last 2 years, 6 months ago hoarseness began to appear gradually and has persisted cyanosis, large liver, heart disease of rheumatic origin for past 7 years deep cyanosis, large liver, edema.	Equal, irregular	Heart enlarged, bulging in region of left auricle	None	Discharged against advice, not heard from
3	48	F	Mitral stenosis, auricular fibrillation	For 15 years heart disease of rheumatic origin, 9 months ago edema, etc in bed since 5 days ago hoarse, slight cyanosis edem.	Absolute arrhythmia	Hydropneumothorax, heart displaced to left	Mitral stenosis, hydropericardium, arteriosclerosis of aorta and pulmonary artery, chronic pleuritis	Electrocardiogram fibrillation, right ventricular preponderance Right pupil larger than left
4	40	F	Mitral stenosis of aorto-pulmonary artery		Dilated heart, limited excursion, adherent pericarditis		None	Partial paralysis of left cord, patient died
5	12	M	Mitral stenosis and insufficiency	Heart disease since 2 years cough with expectoration dyspnea, adherent pericarditis, large liver, pericarditis sudden onset of heart disease 3 years ago, since then dyspnea on exertion, often orthopnea, 10 months ago hoarse following bronchitis, light cyanosis and edema of shins	Right and left heart enlarged, bulging of heart shadow at 2d interspace which does not correspond to aortic arch and is probably left auricle		None	First and second sounds reduplicated, complete paralysis of left cord, discharged unrelieved
6	26	F	Mitral stenosis		General enlargement of heart shadow, especially of left side		None	Left cord completely paralyzed
7	12	M	Mitral stenosis and insufficiency Adherent pericarditis (?)	One year ago, fever, dyspnea, palpitation, orthopnea	General enlargement of heart shadow		None	Left cord completely paralyzed
8	15	F	Mitral stenosis and insufficiency Adherent pericarditis (?)	Two years heart disease, and dyspnea on exertion since, worse the last 4 months, edema of feet and hoarseness, cyanosis, large liver, "compensation poor," died 1 year later	Small absolutely irregular		None	Patient discharged unrelieved
9	22	F	Mitral stenosis, aortic insufficiency	Six months ago hand cold with blood stained spurtum, 2 months ago lost voice but was hoarse some time before this, decompenation followed	Synchronous	Heart dilated, both auricular regions prominent	None	

Onset and Course of Hoarseness—In some of the reported cases the onset of hoarseness was sudden, often occurring in the course of a walk. In all of such instances the onset occurred simultaneously with dyspneic attacks. Carrau, however, reported a case in which the patient had “the crisis of her heart disease without paralysis, and only six months before the termination of the crisis and without indication of the broken heart compensation, she lost her voice.” Most of these patients show a rapid improvement to normal which may or may not be permanent. But they may show one or more recurrences coincident with cardiac crises, and the paralysis may finally become permanent in a complete or partial form.

In most cases, however, hoarseness comes on gradually. Its course is usually slow and progressive until a maximum is reached and remains permanent irrespective of cardiac improvement.

A few patients show marked improvement of the voice, the voice even becoming normal, but on examination it is found that this is not due to increased movement of the affected cord but to the accommodation of the sound one.

Change of position may, but does not always, influence the hoarseness. Proto found that in his patient rotation of the head in different positions produced a change in the voice. In Hofbauer's first case the voice became more hoarse with the patient lying on the left side or when bending forward. In the case of Lian and Marcolles the left lateral decubitus produced more marked hoarseness, while Carrau's patient showed a similar change when lying down in any position, but not on rotation of the head. All these cases were mild, and the onset was fairly rapid.

Hofbauer explained by Kraus' theory that in certain positions the aorta is pulled down more than in others, and hence stretching of the nerve is greater. The view of Lian and Marcolles is that in decubitus there is increased contact between the left auricle and the pulmonary artery and therefore between the latter and the nerve. Frestadtl and Stranz take exception to the reports of alteration in the quality of the voice with postural changes, because in their cases in which postmortem examination was made they found degeneration of the nerve and of the muscles supplied by that nerve, and therefore change of the voice was impossible. But it is clear from the facts given above that all cases of paralysis are not similar, since their onset and course and probably their etiology, differ. When the onset is gradual and progressive with degenerative changes in the nerve, vocal changes with posture cannot occur, whereas it is probable that paralyses of sudden onset and rapid improvement are due to a neuritis caused by mechanical disturbance in the mediastinum (as by the continuous pulsation of the pulmonary artery against the nerve, etc.), thus making the nerve more

sensitive to pressure, which varies on change of position, and with the change in pressure, alteration in the character of the voice occurs. This view corresponds to that of Lian and Marcolles, who explain recurrence of paralyses with cardiac crises by the pressure of the acutely enlarged heart upon the sensitive nerve.

The duration of hoarseness varies with the type of paralysis. Where it is acute and due at least partly to a neuritis, it improves in from a few days to two or three months, provided the cardiac condition improves and pressure paralysis does not supervene. When paralysis is complete, there is no change in the voice except so far as the sound cord can compensate. These facts are borne out by necropsy reports. The cases of Ortner, Osler (Case 3), Kraus and Von Schroetter, with permanent paralysis lasting for a year or more before death, showed microscopic degeneration of the nerve, that of Mead with paralysis of one month's duration showed no degeneration.

Quadrone reports seven cases in which there was bilateral paresis. He explains by Kraus' theory that where the descent of the aortic arch is so great as to affect the right subclavian vein, the right recurrent nerve becomes stretched in the descent of that vein. Ceraulo also reports a case of double paralysis.

DIAGNOSIS

An interesting and important point is the differentiation of these cases from aortic aneurysm, and undoubtedly such cases were diagnosed as aneurysm before the aid of the roentgen ray and before Ortner pointed out a hitherto unknown etiology.

Ortner, Nothnagle and Osler, in their first cases, made a diagnosis during life of aortic aneurysm, and only at necropsy was the true condition revealed. Ortner laid stress on the difference in the carotid pulses, the left being smaller than the right. Osler's opinion was influenced mainly by symptoms of dyspnea and cyanosis without edema and the presence of a diffuse precordial impulse reaching to the second intercostal space.

The difference in pulses has been noticed in other cases. Alexander, Hall, Ceraulo, Quadrone, and Fetterolf and Norris found the left pulse smaller than the right. Dmitrenko, and Guttman and Neuhoff noted that the blood pressure in the right brachial artery was greater than in the left.

Quadrone explains this difference to be due to traction on and constriction of the right subclavian artery. Ortner could not explain it, while Popoff states that it is due to pressure of a contracting cicatrix on the larger vessels.

A misleading sign is the cardiac pulsation in the area of the second costal cartilage. This may spread to the third and fourth spaces. Nine

of the reported cases show this condition Alexander, Dmitrenko, Lian and Marcolles and others by tracings and radioscopy examinations have been able to demonstrate intra vitam that this pulsatile shadow was due to the pulsations of the pulmonary artery, which in many cases was found to be enlarged to the diameter of the aorta and even larger

Inequality of pupils which is sometimes present strengthens the suspicion of aneurysm Three cases are reported with the right pupil larger than the left and two with the left larger than the right

Carrau diagnosed pressure of a dilated auricle on the pulmonary artery by the presence of systolic souffle propagated upward at the pulmonary area

The difficulty of diagnosis is readily seen, and, with the presence of abnormal dulness about the second and third spaces, as found by Perotta and others, the picture of aneurysm is complete We have therefore often to depend almost entirely on the roentgen ray for diagnosis in these cases

AGE AND SEX

De Haviland Hall pointed out that aneurysm is rare before the age of 25, and in women it is one eighth as frequent as in men From the tables of Avellis, Permewan points out that paralysis of the recurrent nerve due to various causes occurs more than twice as frequently in men as in women In the list of cases of paralysis of the nerve in mitral stenosis twenty are male and forty-three female and according to the age period, distributed as shown below

Age	Up to 25	25-30	30-40	40-50	50-55
No of cases	20	30	10	8	2

From this it may be seen that the age and sex of the patient may be an aid in diagnosis If the patient with paralysis of the left recurrent laryngeal nerve is a male and below 25, the paralysis is probably due to a cardiac cause, and also in females even if above 25 years of age

TREATMENT

Digitalis in the early stages, before the nerve becomes degenerated, is useful in distinguishing between cardiac and aneurysmal compression In Carrau's case with sudden hoarseness immediate use of digitalis produced excellent results, both cardiac and vocal conditions improving considerably Of course when the paralysis is of long standing such improvement is impossible

CONCLUSIONS

It is clear that paralysis of the recurrent laryngeal nerve in mitral stenosis may be produced in various ways, and that in a single case there may be more than one etiologic factor

It seems probable that the most important and most frequent mechanism is that of the enlarged pulmonary artery, through its own dilatation, or through the pressure transmitted to it by the left auricle and pulmonary vein, compressing the nerve against the aorta or ductus arteriosus.

Secondary factors may aid in the compression by increasing the rigidity of the opposing parts, namely, thrombi in the auricle, thrombosis of the pulmonary artery, atheroma and sclerosis of the pulmonary artery and aorta, cicatrization, etc.

In a certain number of cases there is probably an initial neuritis, and if the cardiac condition is not improved, the irritability and the increased pressure would the more readily lead to degeneration of the nerve.

Cases occur in which the etiologic factor is enlarged mediastinal glands, etc., coincident with initial stenosis, but even in these cases the heart may play a secondary part.

The importance of fluoroscopic examination must be emphasized, since it often affords the only distinction from aortic aneurysm.

The early use of digitalis both from the point of view of diagnosis and treatment is important.

It is interesting to note the comparative youth of the majority of the patients and its greater frequency in females, both of which observations are an aid in diagnosis.

Laryngoscopic examinations are important in eliminating any local cause of hoarseness, in making out the extent of paralysis, and in determining whether improvement of the voice is due to improvement of paralysis or to the accommodation of the sound cord.

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THE CREATININ TEST FOR RENAL FUNCTION*

RALPH H MAJOR, M.D.

KANSAS CITY, KAN

In a previous communication,¹ attention was directed to certain advantages in the use of creatinin as a test for renal function. This substance, which is apparently an end-product of metabolism, is excreted by the normal kidney with great ease, and its excretion, as emphasized by Schaffer,² is remarkably constant for the same person.

In the series of cases reported, it was pointed out that while normal kidneys responded promptly to an excess of creatinin in the circulation by a greatly increased urinary output of creatinin, the kidneys in chronic nephritis showed no such marked increase, and at times even showed a decrease. As a convenient method of studying the creatinin excretion, the patient's urine was first collected for the period of one hour and the patient then given 0.5 gm of creatinin intravenously. Subsequent collections of urine were made at the end of one hour and at the end of two hours, and the total excretion of creatinin in each of these specimens compared with the hourly excretion before the patient received the creatinin injection.

In this study the same general method has been followed, but in addition observations have been made on the variations in the concentration of creatinin in the urine, the excretion of creatinin during fifteen minute periods has also been studied. In all instances, for the sake of comparison, the phenolsulphonephthalein test has been employed.

Some of the cases reported previously are included in the statistical summary in this paper. In all, the creatinin test has been carried out on 113 persons, including thirty-three with cases of chronic nephritis, thirty with arterial hypertension, seven with marked cardiac decompensation and twenty-five with diabetes mellitus.

METHODS

In most of the earlier tests the creatinin was prepared fresh before using, 0.5 gm being dissolved in 5 cc of distilled water and autoclaved just before injection. In some of the later tests we have used creatinin dissolved in a buffer solution consisting of 27 parts of primary potas-

* From the Department of Internal Medicine, University of Kansas School of Medicine, Kansas City, Kansas.

1 Major, Ralph H. The Use of Creatinin as a Test of Renal Function, J A M A 80: 384 (Feb 10) 1923.

2 Schaffer, Philip. Protein Metabolism in Exophthalmic Goiter, J Biol Chem 3: 13, 1907.

sium phosphate and 73 parts of secondary sodium phosphate, having a p_H value of 7.2. In this solution, a colorimetric reading shows no deterioration of the creatinin for a period of six months. We have found it convenient to put up such a solution in ampules of 5 c.c., each ampule containing 0.5 gm of creatinin and being ready for immediate use.

The creatinin content of the urine has been determined by the method of Folin, using in most instances a Dubosc colorimeter. The simple colorimeter devised by Myers³ has also proved satisfactory for the estimation of creatinin.

In the majority of the tests, the first hour's and the second hour's excretion of creatinin after the intravenous injection of 0.5 gm of creatinin has been compared with the excretion for one hour before the injection. In another series of tests the excretion of creatinin over fifteen minute intervals after injection has been compared with the

TABLE 1—Average Creatinin Excretion in Normal and in Diseased Persons

Group	Creatinin Excretion	One Hour Before Injection	First Hour After Injection	Second Hour After Injection
Normal	Total in milligrams	64	214	113
	Milligrams per 100 c.c.	158	346	195
Cardiac diseases	Total in milligrams	42	127	107
	Milligrams per 100 c.c.	100	283	189
Diabetes mellitus	Total in milligrams	57	168	130
	Milligrams per 100 c.c.	115	215	110
Arterial hypertension	Total in milligrams	49	159	96
	Milligrams per 100 c.c.	134	286	189

excretion for a period of fifteen minutes before. The latter method has not proved reliable unless the urine is collected by catheter, but it may find a useful application when it is necessary to carry out the test in a short time and when it is desirable to study the excretory function of each kidney separately.

It is necessary in all tests to use extreme care that the bladder is emptied completely at the time of each collection of urine. To promote as free a flow of urine as possible, the patient is given a glass of water (150 c.c.) after each voiding.

The Excretion of Creatinin at Intervals of One Hour.—Twelve normal persons were first studied and then the results obtained in patients suffering from a variety of diseases, this series including five cases of cardiac decompensation, ten cases of diabetes mellitus and twenty cases of arterial hypertension. The average excretion in this group is shown in Table 1.

3 Myers, V C. A Simple Colorimeter for Clinical Purposes, J Lab & Clin Med 1 760 1916

This table shows that in this series the total excretion of creatinin one hour after injection is more than twice that of the hour preceding injection, and if the cardiac group is excluded, the excretion at the end of one hour is three times as great as before injection. The total excretion of creatinin at the end of the second hour also averages more than twice that of the hour preceding injection, although in some groups it falls slightly below this average.

The excretion of creatinin in milligrams per hundred cubic centimeters, which is an index of the concentrating ability of the kidneys, at the end of one hour is more than twice that of the hour preceding injection, while at the end of the second hour the increase is not so great.

TABLE 2.—*Creatinin Excretion in Twenty-Five Cases of Chronic Nephritis After Injection of Creatinin**

Blood	Creatinin	Before Injection		1 Hour After Injection		2 Hours After Injection		Phenol sulphone-phthalein		Remarks
		Total	Per 100 C c	Total	Per 100 C c	Total	Per 100 C c	Percentage		
1	22	1.8	70	59	63	71	71	43		
2	16	1.5	27	183	8	98	38	40	Died 1 year of uremia	
3	81	5.0	36	70	7	18	19	7		
4	12	1.7	30	123	54	129	50	18	Died 6 months later	
5	20	1.0	56	70	0	0	142	40		
6	11	2.0	16	30	12	27	12	26	Trace	Died, necropsy
7	26	1.5	91	201	122	102	95	30		
8	46	2.7	45	90	46	70	70	47	Trace	Died, necropsy
9	13	1.2	37	83	17	105	31	50		
10	14	2.3	43	112	63	180	66	40		
11	17	2.8	138	153	179	256	44	22		
12	20	2.0	30	103	39	133	25	15	Died 3 months later	
13	22	1.5	25	125	9	44	40	25		
14	46	4.2	48	44	60	47	64	3	Died 2 months later	
15	25	2.6	86	284	125	125	119	30		
16	37	1.5	75	35	88	42	60	15		
17	60	2.4	50	99	55	109	80	15	Died, necropsy	
18	81	7.0	17	58	26	58	25	5	Died, necropsy	
19	21	1.5	75	108	57	320	53	534	Died, necropsy	
20	40	6.6	99	142	118	157	193	7		
21	37	2.8	32	71	8	50	50	6		
22	15	1.5	74	124	109	218	110	35		
23	15	1.9	91	118	121	338	118	45	Died 2 months later, necropsy	
24	35	2.3	80	100	102	164	35	12		
25	32	2.0	74	41	92	77	63	45		

* Urine was collected at one hour intervals. Creatinin excretion is expressed in milligrams blood urea and blood creatinin are expressed in milligrams per 100 C c.

A study of the group of twenty-five cases of chronic nephritis shows a very different behavior in the excretion of creatinin following injection. This group is of especial interest, and the results are charted in some detail in Table 2. All of these patients were clear-cut examples of patients with chronic nephritis, and an arterial hypertension was present. Six of the patients came to necropsy. One patient died while under observation, but necropsy was not performed, and three patients died after discharge from the hospital.

A study of this table shows that in chronic nephritis the kidneys do not respond to the increased creatinin content of the blood by an increase in the output amounting to two or three times that excreted before

injection. In eight patients the total amount of creatinin excreted during the hour period after injection was less than the amount excreted during the hour before injection. This is a striking finding and indicates that while the normal kidney responds promptly to the increased amount of creatinin in the blood, this increase may in disease exert a partially paralyzing effect on the kidney so that it excretes less than before (Fig. 1).

The excretion of creatinin in terms of milligrams per 100 cubic centimeters follows much the same course in these cases of chronic

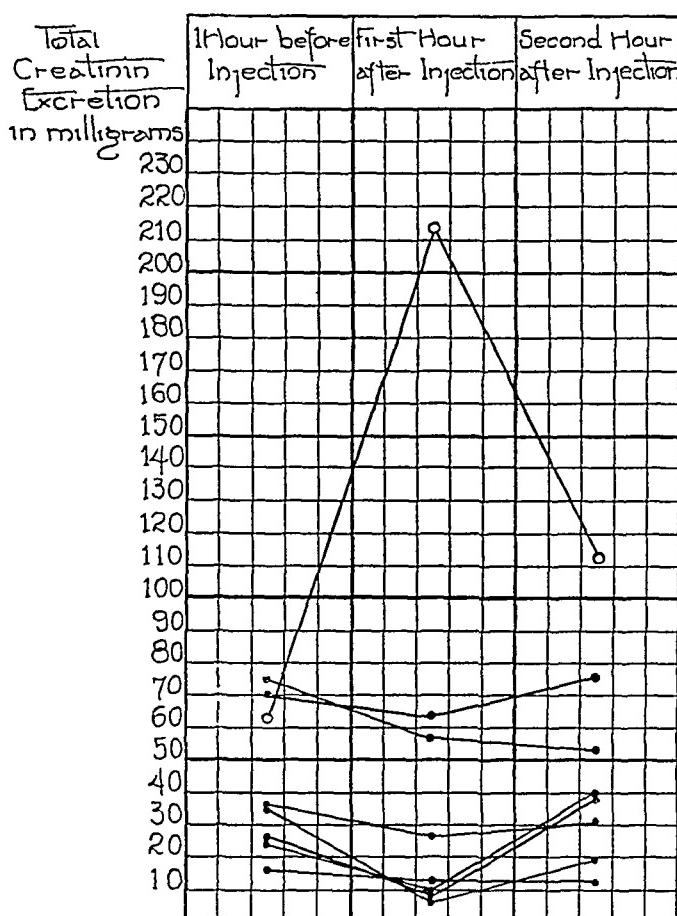


Chart 1—Creatinin excretion in seven cases of chronic nephritis. Note depression following intravenous injection of creatinin. A curve showing the average excretion in twelve normal controls is superimposed on the table. The line and hollow dots indicate the average normal excretion, the line and solid dots indicate chronic nephritis.

nephritis as does the total excretion. Here again the average creatinin concentration in the urine is only slightly increased one hour after the injection, and in eight instances it was actually less than before.

The phenolsulphonephthalein excretion in most of these patients was markedly decreased, although there were a few exceptions. Patient

No 2, who excreted 40 per cent in two hours, died two weeks later of uremia, and Patient No 23, who excreted 45 per cent phenol-sulphonephthalein in two hours, died two months later. Both of these patients showed the nephritic type of creatinin curve, and the diagnosis of chronic nephritis was confirmed by necropsy in Patient No 23.

A comparison between the type of curves obtained in chronic nephritis and those in other conditions is shown in Charts 1 and 2.

The Excretion of Creatinin at Intervals of Fifteen Minutes—In order to shorten the time necessary for carrying out the creatinin test, a series of observations were made on patients, examining the urine at

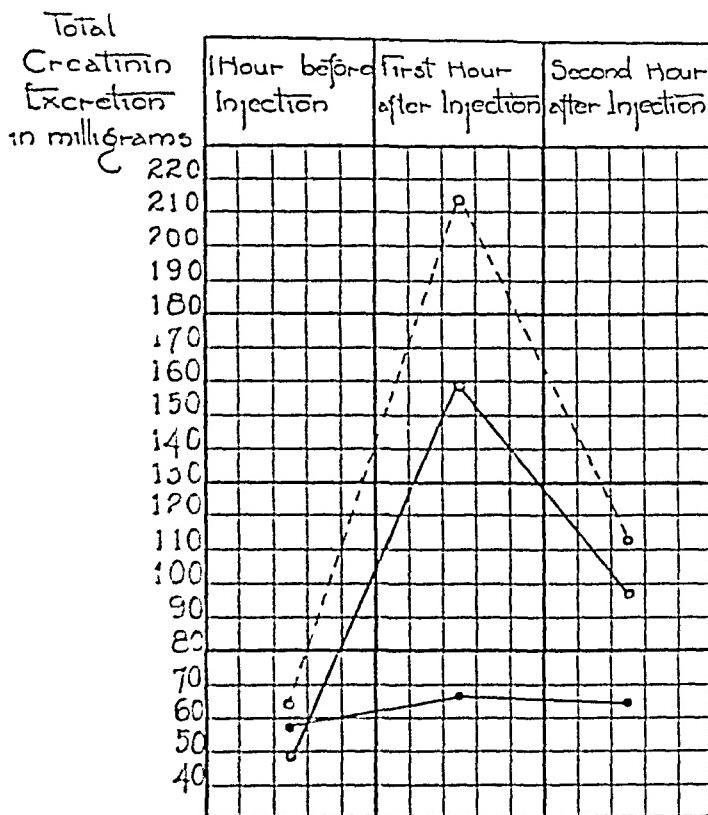


Chart 2—Average total creatinin excretion in three groups of cases, hour periods. The broken line and hollow dots indicate normal, the continuous line and hollow dots, arterial hypertension, the continuous line and solid dots, chronic nephritis.

quarter hour periods instead of at the end of each hour. It was found early in the use of this method that slight delays in the collection of the urine or failure to empty the bladder completely made the results inaccurate. In order to avoid these sources of error, we catheterized our patients, and the catheter was kept in the bladder until the conclusion of the test.

This series comprises a smaller group of cases consisting of eight cases of chronic nephritis, ten cases of arterial hypertension and eight cases of diabetic mellitus. The urine in each instance was collected

first for fifteen minutes, then 0.5 gm creatinin was injected intravenously and the urine collected at fifteen minute periods for one hour. The patient received a glass of water (150 cc) fifteen minutes before each collection of urine. The results in terms of total creatinin excretion are shown in Figure 4, while the ability of the kidney to concentrate and excrete the creatinin is shown in Figure 5.

A study of the curve of total creatinin excretion shows that using fifteen minute periods of observation, the kidneys in chronic nephritis are unable to respond to the intravenous injection of creatinin by any marked increase in excretion. In the two other conditions studied which were accompanied by no evidence of renal lesions, the injection

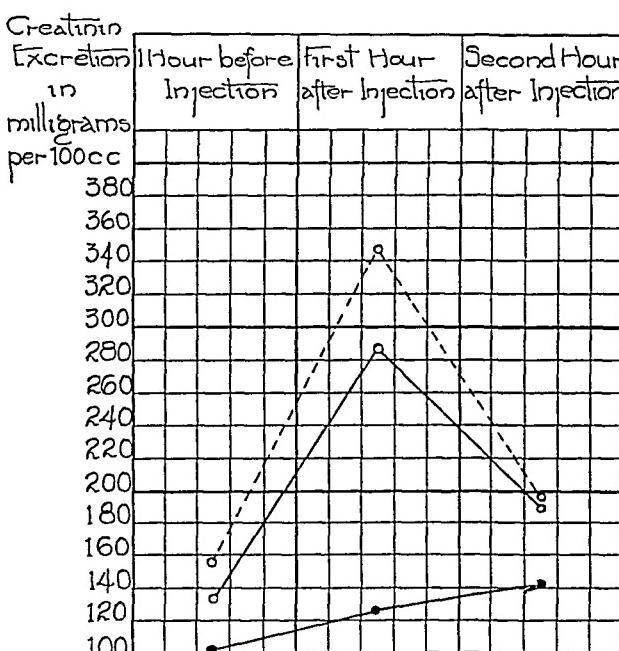


Chart 3—Average excretion of creatinin in milligrams per 100 cc of urine, in same patients as in Chart 2. The broken line and hollow dots indicate normal, the continuous line and hollow dots, arterial hypertension, the continuous line and solid dots, chronic nephritis.

of creatinin was followed by a marked increase in output, the average for the first fifteen minute period after injection being three times that of the same period before injection.

The curve of urinary creatinin concentration in Figure 5 shows that while patients with diabetes and arterial hypertension respond with an immediate marked increase in concentration, followed by a fall, the nephritic patients show marked delay in this response.

This method of studying the creatinin excretion in fifteen minute periods is being used at this clinic for certain selected cases. While our experience with it is not as great as with the method of hourly collec-

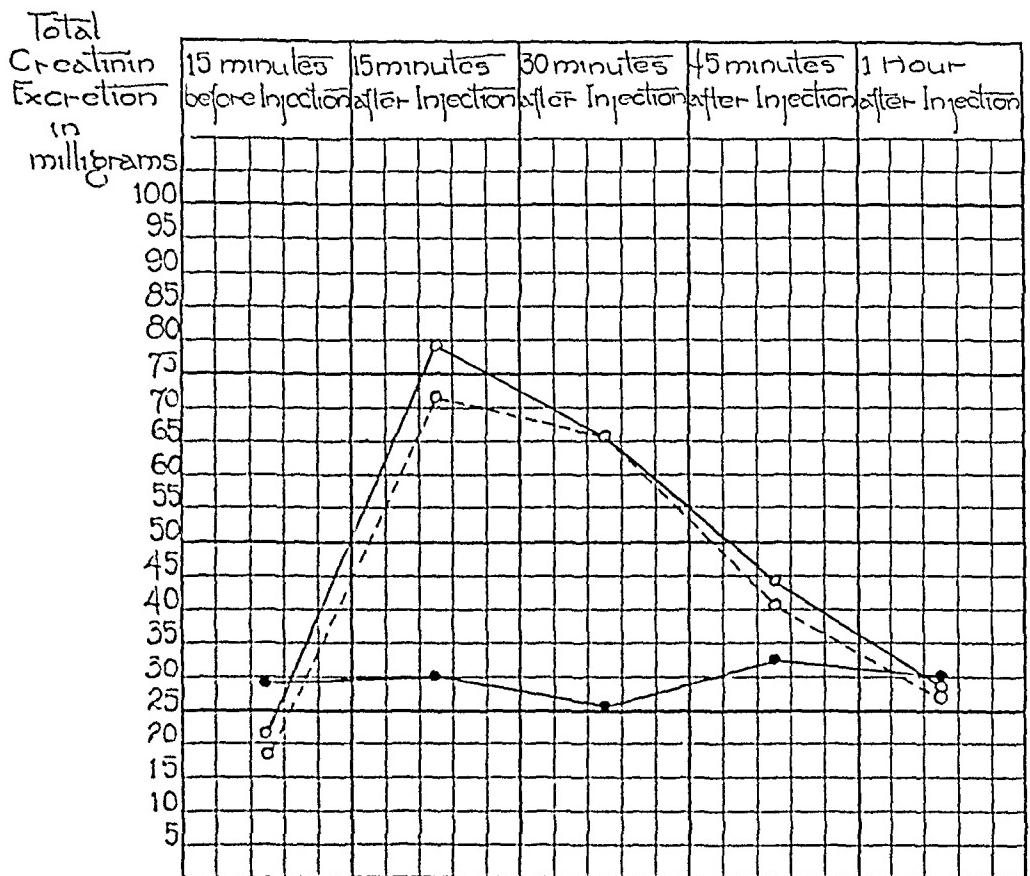


Chart 4—Average total creatinin excretion over fifteen minute periods. The solid line and hollow dots indicate arterial hypertension, the broken line and hollow dots, diabetes mellitus, the continuous line and solid dots, chronic nephritis

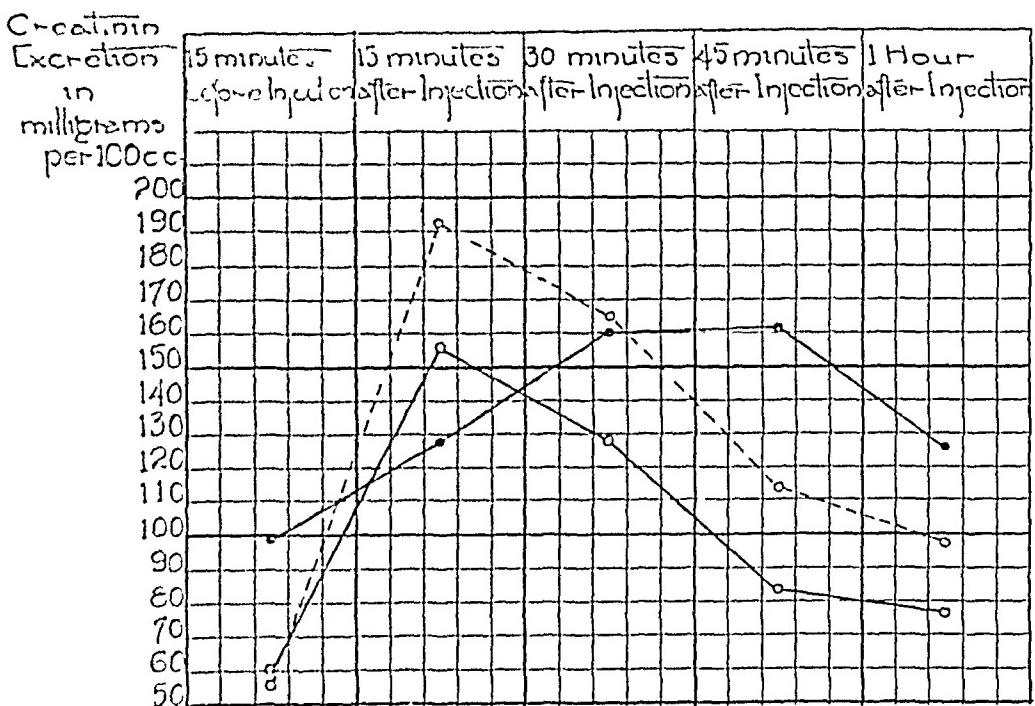


Chart 5—Average excretion of creatinin in milligrams per 100 cc of urine over fifteen minute periods, same patients as in Chart 4. The broken line and hollow dots indicate diabetes mellitus, the continuous line and solid dots, chronic nephritis, the continuous line and hollow dots, arterial hypertension

tions, it appears to be reliable when properly carried out, and may prove of great value in studying the functional capacity of the individual kidney.

CONCLUSIONS

The creatinin test as described in this paper has proved to be a good index of kidney function in disease.

The normal kidneys respond to the intravenous injection of creatinin by an increased output of creatinin which averages three times that excreted during the same period of time.

The kidneys in chronic nephritis show on the average only a slight increase. In many instances a decrease was observed.

THE EXCRETION OF ORGANIC ACIDS IN THE URINE OF PATIENTS WITH DIABETES MELLITUS *

P A U L S T A R R , M D , A N D R E G I N A L D F I T Z , M D
B O S T O N

Several observers have described cases of diabetes mellitus in which there appeared to be severe acidosis but in which there was no evidence in the urine of the presence of acetone bodies. Such cases have been described for example, by Stadelmann¹ in 1883, by Freichs² in 1884, by Lepine³ in 1909, by Revillet⁴ in 1914, by Rosenbloom⁵ in 1915, by McCaskey⁶ in 1916 and more recently by Bock, Field and Adair⁷ in 1923. These isolated observations have suggested the possibility that other acids than the acetone bodies may play a part in the production of diabetic acidosis, and have led us to study the urine of a series of diabetic patients to determine whether other organic acids than the ketones are ever excreted in any significant amounts. This paper records the results of this work.

We have used the following method. Mixed twenty-four hour samples of urine preserved with toluol or flesh single specimens were used for each analysis. The total organic acid concentration was determined by the method of Van Slyke and Palmer⁸. The acetone body concentration, including acetone, diacetic and beta-hydroxybutyric acid, was determined by the gravimetric method of Van Slyke⁹. From these analyses we were able to fraction the organic acidity of any urine into two parts the first fraction being the one due to the acetone bodies, and the second being due to undetermined organic acid or acids. In several samples we determined the creatin and creatinin content by Folin's¹⁰

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston

1 Stadelmann, E. Ueber die Ursachen der pathologischen Ammoniakausscheidung beim Diabetes Mellitus und des Coma diabeticum, Arch f experimentelle Pathol **17** 419-444, 1883

2 Von Frerichs, F. T. Ueber den Diabetes, Berlin August Hirschwald, 1884, p. 113

3 Lepine, R. Le diabète sucre, Paris, Alcan, 1909

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6 McCaskey, G. W. A Case of Fatal Diabetic Coma Without Diacetic or Beta-Oxobutyric Acid, J. A. M. A. **66** 350-351, 1916

7 Bock, A. V., Field H., Jr., and Adair, G. S. The Acid Base Equilibrium in Diabetic Coma, In press

8 Van Slyke, D. D., and Palmer, W. W. The Titration of Organic Acids in Urine, J. Biol. Chem. **41** 567-585, 1920

9 Van Slyke, D. D. The Determination of B-Hydroxybutyric Acid, Aceto-Acetic Acid, and Acetone in Urine, J. Biol. Chem. **32** 455-493, 1917

10 Folin, O. Laboratory Manual of Biological Chemistry, New York, D. Appleton & Co. 1922

method, as Van Slyke and Palmer point out that these substances may interfere with the total organic acid excretion obtained by their method. We did not find, however, that this analysis was necessary in every case, as the highest creatin and creatinin figures encountered in the

TABLE 1.—*The Organic Acid Excretion in the Urine of Patients with Diabetes Mellitus*

Sample No	C c N/10 Acid per Liter			Sample No	C c N/10 Acid per Liter		
	Total Organic Acid	Total Acetone	Undetermined Acid		Total Organic Acid	Total Acetone	Undetermined Acid
1	1,750	1,380	370	51	620	470	150
2	1,740	1,450	290	52	600	420	180
3	1,480	1,140	340	53	600	350	250
4	1,420	1,140	280	54	600	360	240
5	1,370	1,050	320	55	590	430	160
6	1,320	1,140	180	56	580	410	170
7	1,280	980	300	57	580	150	430
8	1,220	1,040	180	58	580	170	410
9	1,220	1,000	220	59	580	320	260
10	1,180	870	310	60	550	370	180
11	1,180	905	275	61	510	170	370
12	1,170	790	380	62	540	170	300
13	1,110	770	340	63	500	290	210
14	1,080	910	170	64	500	260	240
15	1,060	910	150	65	480	190	290
16	1,040	840	200	66	480	160	320
17	1,020	850	170	67	480	210	270
18	980	800	180	68	460	70	390
19	970	800	170	69	440	240	200
20	970	690	280	70	440	270	170
21	960	650	310	71	420	270	150
22	960	820	140	72	420	270	150
23	960	670	260	73	420	60	360
24	960	790	170	74	420	60	340
25	940	770	170	75	410	300	110
26	910	570	340	76	400	170	230
27	910	570	210	77	400	200	200
28	900	825	75	78	400	125	275
29	870	690	170	79	380	140	240
30	840	700	140	80	380	100	250
31	820	670	150	81	370	190	180
32	820	500	320	82	370	180	190
33	800	710	90	83	360	180	180
34	800	700	100	84	320	80	240
35	800	550	250	85	320	40	280
36	780	410	370	86	300	100	200
37	760	610	150	87	290	110	180
38	750	430	320	88	280	50	230
39	720	480	240	89	280	200	80
40	720	470	250	90	260	40	220
41	720	460	260	91	250	25	225
42	700	310	390	92	250	50	200
43	700	340	360	93	220	60	160
44	700	570	130	94	220	0	220
45	680	300	380	95	220	70	150
46	670	450	220	96	200	40	160
47	670	420	250	97	200	20	180
48	670	500	170	98	200	10	190
49	660	440	220	99	190	35	155
50	640	300	340	100	170	70	100
Average							233

* Urines in which the undetermined fraction was less than 450 c c per liter.

urines containing most nitrogen did not account for any large proportion of the total urinary acidity. We expressed our results in terms of decinormal organic acid or total acetone per liter of urine.

We analyzed in this fashion a series of 114 urine samples obtained from eighteen diabetic patients with varying degrees of acidosis, divid-

ing the results into two groups. Group 1 contains those urines of varying degrees of acidity in which the undetermined organic acid fraction was 450 cc or less per liter. Group 2 contains those diabetic urines of varying degrees of acidity in which the undetermined organic acid fraction was more than 450 cc per liter. We divided our results in this arbitrary fashion because Van Slyke and Palmer's figures for thirteen normal men show that the average normal organic acid excretion does not exceed 450 cc per liter of urine. The results of these analyses are recorded in Tables 1 and 2.

As can be seen by Table 1, 100 of the 114 samples of urine, or 88 per cent, had an unidentified organic acid excretion of less than 450 cc to the liter. In this series the unidentified acidity varied between 430 and 75 cc to the liter, while the average was 233 cc. Those urines with the highest total acidity contained the most acetone bodies, and the

TABLE 2.—*The Organic Acid Excretion in the Urine of Patients with Diabetes Mellitus**

Sample No	Cc N/10 Acid per Liter		
	Total Organic Acid	Total Acetone	Undetermined Acid
1	2,970	40	2,930
2	1,620	1,100	520
3	1,540	870	670
4	1,460	885	575
5	1,460	860	600
6	1,440	945	495
7	1,380	150	1,230
8	1,160	675	485
9	1,120	420	700
10	1,100	220	880
11	960	0	960
12	880	140	740
13	800	330	470
14	610	109	501

* Urines in which the undetermined fraction was more than 450 cc per liter.

parallelism between the excretion of the total organic acids and acetone bodies was striking. Van Slyke and Palmer have already mentioned that the organic acid titration in diabetic urines is so parallel to the acetone body analyses that the rise above the normal output in organic acid excretion may be used as an approximate measure of the acetone body excretion. So far as we can determine from the literature, the method has not come into general clinical use in this country for this purpose except at the Montreal General Hospital, where Rabinovitch¹¹ reports satisfactory results with it. Our data show that by subtracting the average undetermined acid figure of 230 from any one of the total organic acid readings, we obtained a fair index of the total acetone concentration, especially in cases in which this was high enough to be of any clinical significance. This point is important for people doing

¹¹ Rabinovitch, I. M. A Simple Method for Determining the Approximate Degree of Acidosis in Diabetes Mellitus, *Canad. M. J.* **11**: 526-528, 1921.

routine diabetic laboratory work, as the organic acid titration is simple and easy to perform, whereas the total acetone estimation is more time consuming and requires more apparatus.

Table 2 records the fourteen urine samples from four cases which contained more than 450 cc of unidentified organic acid to the liter. The unidentified fraction varied from 485 cc to 2,930 cc. The urine of one of Van Slyke and Palmer's normal men contained 740 cc of tenth normal organic acids to the liter. If we exclude all the urines in Table 2 with readings below this point on the ground that they might contain no more than normal amounts of acid, there still remain four samples from two cases of coma with so high a concentration of unidentified organic acid as to bring up the question whether such acid or acids may not have produced clinical symptoms of acidosis, and may not have played a part in producing the clinical picture of diabetic coma.

If other acids than the ketones produce diabetic acidosis, they should be recognizable not only in the urine but also should manifest themselves in the blood. Our next step, therefore, was the attempt to discover the presence of such acids by fractionating the acid content of the blood from cases with diabetic acidosis as we fractioned the acidity of the urine. For this purpose we have made use of an indirect method open to certain obvious objections, but one which has yielded interesting results.

Fitz and Van Slyke¹² estimated in their studies on the alkaline reserve and acid excretion that the acid retained in the blood could be rationally expressed by the following formula:

$$\text{Retained acid} = 80 - \text{plasma CO}_2$$

They used this expression because they found that when the plasma carbon dioxide reached 80 volumes per cent the urinary acidity to phenolphthalein and the ammonia excretion approached zero, while as the plasma carbon dioxide fell below this point the excretion of free and combined acids increased proportionally. From this they concluded that there was a definite relationship between acids retained in the blood and acids excreted in the urine and that when the blood carbon dioxide was 80 volumes per cent there was a negligible amount of acid in the blood and therefore no excretion of acid in the urine.

Van Slyke, Stillman and Cullen¹³ have demonstrated that the molecular concentration of carbon dioxide in any plasma can be found by dividing the volumes per cent of carbon dioxide as determined by Van Slyke's method by 2,240.

12 Fitz, R., and Van Slyke, D. D. The Relationship Between Alkaline Reserve and Acid Excretion, *J. Biol. Chem.* **30** 389-400, 1917.

13 Van Slyke, D. D., Stillman, E., and Cullen, G. E. A Method for Titrating the Bicarbonate Content of the Plasma, *J. Biol. Chem.* **38** 167-178, 1919.

Assuming that acids retained in the blood displace carbon dioxide in ratio to their molecular concentration, and accepting Fitz and Van Slyke's figures, the "retained acid" of the blood can be expressed as follows

$$\text{Molecular concentration of retained acid} = 0.0357 - \frac{\text{CO}_2}{2,240}$$

We used this formula and determined in this fashion the molecular concentration of the total "acid retained in the blood" in a series of fifty-two blood samples from twelve cases of diabetes. We obtained at the same time the molecular concentration of the acetone bodies in these bloods including acetone, diacetic acid and beta-hydroxybutyric acid by the gravimetric method of Van Slyke and Fitz¹⁴ thus we were able to fraction indirectly the "retained acid" of these bloods into two parts, the first fraction being the one due to the acetone bodies and the second being due to undetermined acid or acids.

We have arbitrarily divided the results of these analyses into two groups. The first group contains the bloods with an unidentified "retained acid" of concentration less than 0.0135 M. The second group contains the bloods with an unidentified "retained acid" of concentration greater than this figure. We have selected this figure as a dividing point because acetone free bloods with a carbon dioxide combining power of less than 50 volumes per cent will necessarily have a "retained acid" of greater concentration than 0.0135 M, and plasmas with carbon dioxide capacities below this point are ordinarily supposed to be indicative of acidosis.

As can be seen forty-six bloods, or 88 per cent of the samples studied, fall in Group 1, the average undetermined "retained acid" having a molecular concentration of 0.0072, the maximum "retained acid" being 0.0135 M and the minimum being zero. It is of interest, however, that the variation in unidentified "retained acid" should have been so relatively slight considering that the blood samples represented degrees of acidosis from 12.8 volumes per cent of carbon dioxide to normal, and degrees of acetonemia from over 100 mg of total acetone per 100 cc of blood to less than 10 mg. Furthermore, the average molecular concentration of "unidentified retained acid" was 0.0072 M, which would correspond to an alkali reserve of 80—16.1, or 63.9 volumes per cent, which is a normal figure.

Table 4 includes the six blood samples with an unidentified "retained acid" of a concentration greater than 0.0135 M. The figures vary between 0.0148 and 0.0205 M. They appear to be of greater significance if the effect of the "unidentified retained acid" on the plasma bicarbonate is estimated. The blood with the lowest undetermined "retained acid" represents one having an acidosis of 80—32.5, or 47.5 volumes

¹⁴ Van Slyke, D. D., and Fitz, R. The Determination of B-Hydroxybutyric Acid, Aceto-Acetic Acid, and Acetone in Blood, *J. Biol. Chem.* **32**, 495-497, 1917.

per cent of carbon dioxid, a figure on the lower limits of normal. The blood having the highest undetermined "retained acid" represents one having an acidosis of 80—46 or 34 volumes per cent of carbon dioxid, a figure certainly low enough to be significant.

On the whole, we found from these preliminary observations that about 90 per cent of a series of 114 diabetic urines contained unidentified acid or acids within the concentration limits of organic acids.

TABLE 3—*The "Retained Acid" in the Blood of Patients with Diabetes Mellitus**

Number	Total "Retained Acid" Molecular	Total Acetone Bodies Molecular	Undetermined "Retained Acid" Molecular	Number	Total "Retained Acid" Molecular	Total Acetone Bodies Molecular	Undetermined "Retained Acid" Molecular
1	0.0334	0.0240	0.0094	24	0.0148	0.0108	0.0040
2	0.0304	0.0196	0.0108	25	0.0146	0.0084	0.0062
3	0.0285	0.0183	0.0102	26	0.0142	0.0125	0.0017
4	0.0277	0.0213	0.0064	27	0.0137	0.0058	0.0049
5	0.0269	0.0140	0.0129	28	0.0136	0.0071	0.0065
6	0.0240	0.0109	0.0131	29	0.0133	0.0072	0.0061
7	0.0227	0.0123	0.0104	30	0.0129	0.0112	0.0017
8	0.0221	0.0106	0.0115	31	0.0126	0.0057	0.0069
9	0.0219	0.0113	0.0106	32	0.0122	0.0047	0.0075
10	0.0206	0.0072	0.0134	33	0.0112	0.0038	0.0074
11	0.0200	0.0065	0.0135	34	0.0111	0.0046	0.0065
12	0.0194	0.0104	0.0090	35	0.0109	0.0046	0.0063
13	0.0187	0.0123	0.0064	36	0.0103	0.0084	0.0019
14	0.0185	0.0108	0.0077	37	0.0098	0.0088	0.0060
15	0.0182	0.0068	0.0114	38	0.0097	0.0015	0.0082
16	0.0156	0.0063	0.0093	39	0.0094	0.0044	0.0050
17	0.0156	0.0057	0.0099	40	0.0093	0.0053	0.0040
18	0.0152	0.0079	0.0073	41	0.0093	0.0027	0.0060
19	0.0151	0.0070	0.0081	42	0.0091	0.0073	0.0018
20	0.0151	0.0088	0.0063	43	0.0089	0.0090	0.0000
21	0.0151	0.0070	0.0080	44	0.0089	0.0042	0.0047
22	0.0151	0.0147	0.0004	45	0.0084	0.0029	0.0055
23	0.0149	0.0040	0.0109	46	0.0062	0.0053	0.0009

* Bloods in which the undetermined fraction was in a concentration less than 0.0135 M.

TABLE 4—*The "Retained Acid" in the Blood of Patients with Diabetes Mellitus**

Number	Total "Retained Acid" Molecular, per 100 C c	Total Acetone Bodies Molecular, per 100 C c	Undetermined "Retained Acid" Molecular, per 100 C c
1	0.0304	0.0099	0.0205
2	0.0304	0.0156	0.0148
3	0.0317	0.0126	0.0191
4	0.0295	0.0140	0.0145
5	0.0287	0.0108	0.0179
6	0.0198	0.0035	0.0163

* Bloods in which the undetermined fraction was in a concentration more than 0.0135 M.

present in normal urines. About 10 per cent, however, contained organic acid or acids other than the acetone bodies in considerably higher concentration than is ordinarily found in normal urines. About 90 per cent of a series of fifty-two diabetic bloods contained acetone bodies of which the molecular concentration appeared to account for the diminution below 80 volumes per cent of alkali reserve encountered, and in which therefore the unidentified "retained acid" fraction

was insufficient to produce acidosis. About 10 per cent contained an alkali reserve which was far less than could be accounted for by the blood acetone body concentration present, and which therefore had an unidentified "retained acid" fraction which might be a factor in producing symptoms. These facts suggest that in certain cases of diabetic acidosis other acids than the acetone bodies are formed in the body in abnormal amounts and are excreted in the urine.

We have seen clinically at least six cases of diabetes which support this conclusion. Bock, Field and Adam have recently published one of these cases, and four others are reported here. The following case is first discussed by way of control. We believe that it represents the type of diabetic acidosis due solely to acetone bodies and is commonly encountered.

REPORT OF CASES

CASE 1—P. B. B. H., a woman, aged about 50, with diabetes of ten years' duration, entered the hospital Feb 23, 1923, with a plasma carbon dioxide of 19 volumes per cent and appeared critically ill. She was treated with insulin and ordinary dietetic management. The studies on acidosis which were made are recorded in Table 5.

TABLE 5.—*Acidosis in Case 1*

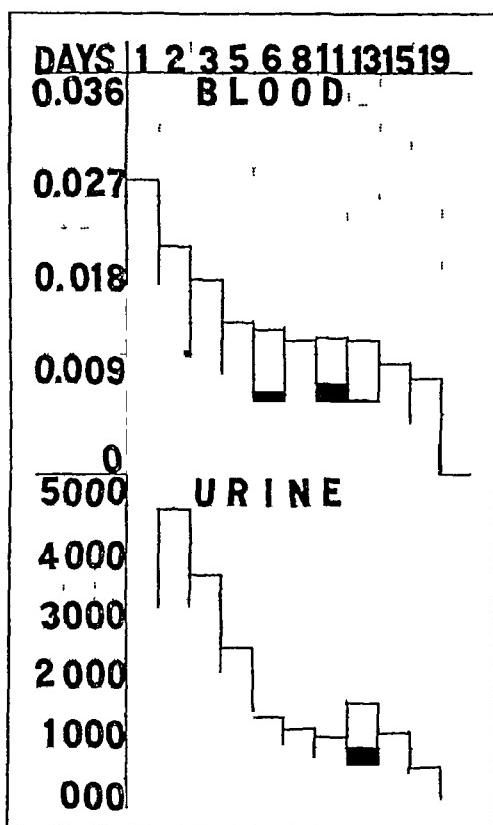
Date, 1923	Urine						Blood			
	Total Organic Acid O c N/10	Total Acetone C e N/10	Total Undetermined Acid, O c N/10	Total Nitrogen, Gm per 24 Hours	"Retained Acid," per 100 O c , Molecular	Total Acetone Bodies, 100 C e , Molecular	Total Undetermined Acid, per 100 O c , Molecular	Total "Retained Acid," per 100 O c , Molecular		
	24 Hours	24 Hours	24 Hours	24 Hours	100 C e , Molecular	100 C e , Molecular	per 100 O c , Molecular	per 100 O c , Molecular		
Feb 23										
24	4,850	3,300	1,550	13.3	0.0284	0.0183	0.0101	0.0101		
25	3,850	2,180	1,670	19.7	0.0227	0.0123	0.0104	0.0104		
27	2,640	1,650	990	10.7	0.0194	0.0104	0.0090	0.0090		
28	1,500	1,120	380	5.6	0.0151	0.0070	0.0081	0.0081		
March 2	1,300	860	440	4.7	0.0147	0.0084	0.0073	0.0073		
5	1,170	710	460	5.1	0.0133	0.0071	0.0062	0.0062		
7	1,740	960	780	5.6	0.0137	0.0088	0.0049	0.0049		
9	1,260	630	630	5.9	0.0136	0.0071	0.0065	0.0065		
13	640	140	500	4.4	0.0111	0.0046	0.0055	0.0055		
					0.0093	0.0027	0.0036	0.0036		

When the "retained acid" of the blood was highest, the excretion of organic acids was highest, and as the "retained acid" of the blood diminished so did the total acid excretion. There was a definite parallelism, also, between the blood acetone concentration and acetone excretion and between the undetermined "retained acid" of the blood and its excretion. These various relationships are shown graphically in the chart.

The fact that the nitrogen excretion was highest when the undetermined organic acid excretion was highest and that it fell as the undetermined organic acid excretion fell, suggests a possible interrelationship between protein catabolism and the acid or acids excreted. In this case the molecular concentration of undetermined "retained acid" in the blood never exceeded 0.0104 M. We do not consider, therefore, that this patient had an acidosis of sufficient degree to influence the alkali reserve caused by acids other than the acetone bodies in spite of the somewhat increased undetermined organic acid excretion during the first few days' observation. On the other hand, we believe that in this case the clinical signs of acidosis were due entirely to the acetone bodies. This case offers a sharp contrast to the four following cases.

CASE 2—A man, aged 49, entered the Massachusetts General Hospital on Feb 2, 1920, in coma and died thirty-six hours later. By way of treatment he was given forced fluids, oatmeal gruel and orange juice. He did not receive alkali. The observations on acidosis obtained are given in Table 6.

As can be seen, the total "retained acid" of the blood increased as coma developed while the acetone fraction diminished. As a result, the undetermined "retained acid" in the blood increased to a point compatible with the production of clinical symptoms. The concentration of unidentified acids in the urine increased as judged by the titratable acidity plus the ammonia figure, while the concentration of acetone bodies in the urine diminished. It seems highly probable, therefore, that this patient died with an increasing acidosis of undetermined cause, the acetone bodies playing a minor part.



The "retained acid" of the blood and the excretion of organic acids in a case of severe diabetic acidosis. The columns represent the molecular concentration of the "retained acid" of the blood or the twenty-four hour excretion of tenth normal organic acids in urine. The solid columns represent the molecular concentration of acetone bodies in the blood or their excretion as tenth normal acid in urine. The white columns represent the molecular concentration of "unidentified retained acid" in the blood and the unidentified tenth normal organic acids excreted in the urine.

CASE 3—A man, aged 22, entered the Massachusetts General Hospital on Feb 6, 1923, in coma and died about thirty hours later. By way of treatment he received forced fluids, oatmeal gruel and orange juice, sodium bicarbonate and insulin. The observations made on his blood and urine are given in Table 7.

The concentration of organic acids excreted in the urine increased steadily despite the fact that the acetone fraction diminished. Thus the undetermined

fraction grew steadily larger. At the first analysis the undetermined "retained acid" figure in the blood was abnormally high and remained elevated despite the fact that the acetone bodies disappeared from the blood. It is possible that the undetermined "retained acid" of the blood was actually greater than appears in the table because of the sodium bicarbonate given, as this would tend to lower the "undetermined retained acid" fraction of the "blood acidity" as we have estimated it. Despite the alkali taken, the patient was in acidosis at the time of death as the plasma carbon dioxide capacity was only 40 volumes per cent, and the acidosis was not due to the acetone bodies.

TABLE 6—Acidosis in Case 2

Date 1920	Urine			Blood		
	Total Organic Acid, C c N/10 per Liter	Total Acetone, C c N/10 per Liter	Total Undetermined Acid, C c N/10 per Liter	Total Retained Acid," per 100 C c , Molecular	Total Acetone Bodies, per 100 C c , Molecular	Total "Retained Acid," per 100 C c Molecular
February entr	8.0	910	— 90	0.0281	0.0212	0.0069
24 hours				0.0304	0.0198	0.0106
36 hours	8.3	550	+303	0.0304	0.0100	0.0204

* In this case the urinary acidity was not titrated by the method of Van Slyke and Palmer; it is the titratable acidity by Folin's method plus the c c of tenth normal ammonia.

TABLE 7—Observations on Blood and Urine in Case 3

Feb 6-8, 1923	Urine			Blood		
	Total Organic Acid, C c N/10 per Liter	Total Acetone, C c N/10 per Liter	Total Undetermined Acid, C c N/10 per Liter	Total "Retained Acid," per 100 C c , Molecular	Total Acetone Bodies, per 100 C c , Molecular	Total "Retained Acid," per 100 C c , Molecular
Entry	1.100	675	483	0.0329	0.0183	0.0246
4 hours				0.0279	0.0129	0.0150
14 hours	1.380	146	1.234	0.0219	0.0004	0.0205
30 hours	1.700	90	1.610	0.0179	0.0000	0.0174

TABLE 8—Blood and Urine Analyses in Case 4

Date, 1923	Urine			Blood		
	Total Organic Acid, C c N/10 per Liter	Total Acetone, C c N/10 per Liter	Total Undetermined Acid, C c N/10 per Liter	Total "Retained Acid," per 100 C c , Molecular	Total Acetone Bodies, per 100 C c , Molecular	Total "Retained Acid," per 100 C c Molecular
April 14	1.160	6.0	7.0	0.0289	0.0100	0.0189

CASE 4—P B B K, a girl, aged 22 entered the hospital on April 14, 1923, in coma. Diabetes was of sixteen months' duration, and she had been receiving insulin at home for two months previous to entry. A week before entry she developed a sore throat and fever with resultant decrease in tolerance and development of acidosis. Her physician continued the administration of insulin and in addition advised forced fluids and a carbohydrate diet. Despite this treatment, acidosis persisted, and she became unconscious twelve hours before being sent to the hospital. She died two hours later blood and urine analyses yielding the results given in Table 8.

As can be seen, there was a marked degree of acidosis with a large undetermined "retained acid" fraction in the blood, showing that the acetonemia was not accountable for the depletion of the alkali reserve which was present. The undetermined acid concentration of the urine was 510 c.c. to the liter, a figure much higher than our average normal. From this evidence we believe that the acidosis present was only in part due to acetone bodies and that other acids than the ketones were a factor in producing death.

CASE 5—P. B. B. H., a woman, aged 53, who entered the hospital on April 5, 1923, had diabetic symptoms of a year's duration. Three weeks before entry she became very weak and thirsty, and on the morning of admission suddenly had an epileptiform convulsion and became unconscious. She was brought to the hospital a few hours later.

The history was not typical of diabetic coma. However, physical examination gave no evidence of any cerebral lesion, lumbar puncture was normal, there were no signs of uremia, and the patient had acidosis, acetonemia, glycosuria, acetonuria and a blood sugar concentration at entry of 0.53 per cent. The observations given in Table 9 were made on acidosis.

The striking feature in this case was the marked degree of acidosis present in the first blood sample without a corresponding blood acetone body concentration, and the presence in the urine throughout of a large proportion of

TABLE 9.—*Acidosis in Case 5*

Date 1923	Urine				Blood		
	Total Organic Acid, C. C. N/10 per Liter	Total Acetone, C. C. N/10 per Liter	Total Undetermined Acid, C. C. N/10 per Liter	"Retained Acid," per 100 C. C. Molecular	Total Acetone Bodies, per 100 C. C., Molecular	Total Undetermined "Retained Acid," per 100 C. C., Molecular	
April 5	790	250	540	0.0251	0.0090	0.0161	
6	900	340	560	0.0159	0.0074	0.0085	
7	1,080	510	520	0.0127	0.0067	0.0060	
9	1,340	680	660	0.0103	0.0051	0.0057	
13	840	430	410	0.0090	0.0051	0.0038	
17	680	230	450	0.0086	0.0029	0.0057	

unidentified organic acid. We believe therefore that in this case, also, other acids than the acetone bodies were in part responsible for the acidosis present. The patient was given insulin and sodium bicarbonate at entry with an almost immediate improvement. After consciousness was regained a few hours later, the subsequent course in the hospital was uneventful.

COMMENT

On the whole, the foregoing data suggest that in certain cases of diabetic acidosis other organic acids than the acetone bodies are encountered, and play a part in the production of symptoms. These acids may be excreted in the urine in larger concentration than found in normal urines. Under these conditions the fall of the plasma bicarbonate below 80 volumes per cent is usually in excess of that accountable for by the concentration of acetone bodies in the blood.

These observations appear to be of both theoretical and practical significance. They are of theoretical significance as one naturally wonders what such organic acids may be and what part they play in the disturbed metabolism of diabetes. We have no information on this point.

These observations are of practical significance for two reasons. The parallelism between the excretion of total organic acids and of the acetone bodies is so striking in the vast majority of instances as to give a fair index of the acetone body excretion. The titration is simple and consumes little time. Therefore it may be used to advantage for routine work when more specific information in regard to the acetone body excretion is required than that afforded by the qualitative diacetic acid or acetone reaction but when highly accurate analyses are not needed. The only objection to the method which we have found is that urines containing large amounts of albumin will give high organic acid titration readings on account of their albumin content. To the best of our knowledge, however, this source of error has not been present in the diabetic urines discussed in this paper. Moreover, a high degree of albuminuria is not often found in diabetic urines.

In the second place, the facts reported are of clinical significance as they suggest that patients with severe diabetic acidosis can be separated into at least two groups. The first group comprises those cases in which the acetone bodies alone appear responsible for the acidosis. In these cases, the unidentified organic acids excreted in the urine are not in excess of normal, the urinary acid excretion consists almost entirely of acetone bodies, and the fall below 80 volumes per cent of the alkali reserve of the plasma corresponds to the molecular concentration of the acetone bodies in the blood. These cases respond satisfactorily to insulin and do not necessarily require alkali. As insulin forces the oxidation of glucose, it checks the formation of the acetone bodies in the body, the accumulation of acetone in the blood diminishes, the alkali reserve increases, the excretion of acetone bodies becomes less, and the clinical picture of acidosis disappears.

The second group comprises those cases in which other acids than the acetone bodies appear to be a factor in producing acidosis. In these cases, the concentration of unidentified organic acids excreted in the urine is in excess of normal, and the fall below 80 volumes per cent of the alkali reserve of the plasma is much greater than can be accounted for by the molecular concentration of the acetone bodies in the blood. These cases appear to require alkali as urgently if not more urgently than they require insulin, since insulin will clear up the acetone body acidosis but may not affect the acidosis due to other acids, and the alkali released by the disappearance of acetone from the blood and tissues may be insufficient to clear up the condition completely.

Severe diabetic acidosis is always a condition of emergency, and the necessary analyses to separate the two types of cases described are time consuming. In the treatment of any given case of severe diabetic acidosis during the critical period, therefore, it seems reasonable to advise the use of insulin, forced fluids, liberal carbohydrate diet, and

small doses (from 15 to 25 gm per day) of sodium bicarbonate as offering the most sensible and hopeful form of therapy. This plan of treatment has already been recently proposed by Campbell,¹⁵ by Bock, Field and Adair, and by Foster¹⁶. The results reported by these workers are sufficiently striking to justify the conclusions drawn. Our results, obtained from a somewhat different point of view, offer confirmatory evidence pointing to what appears to be a rational treatment of severe diabetic acidosis.¹⁷

15 Campbell, W R Ketosis, Acidosis and Coma Treated by Insulin, J Metabolic Res 2: 605-635, 1923

16 Foster, N B Insulin in Diabetic Coma, Reported at the Meeting of the Association of American Physicians, May, 1923

17 The insulin used in this study was insulin-Lilly

THE SPECIFIC GRAVITY OF THE URINE*

HERMAN SHARLIT, M.D., AND WILLIAM G. LYLE, M.D.
NEW YORK

WITH COMMENTS † BY

THOMAS ADDIS, M.D.
SAN FRANCISCO

In a recent number of the ARCHIVES OF INTERNAL MEDICINE¹ appeared a paper by T. Addis and Marjorie G. Foster under a title identical with the one given to this communication, wherein were offered experimental data which seemed to them to lead to the following conclusions

The specific gravity of the urine of normal persons was measured under varying conditions designed to place a strain on the concentrating activity of the kidney. It was found that not even an approximate idea of the work of the kidney in the excretions of solids could be obtained from the results. It is therefore concluded that specific gravity determinations cannot form part of any method intended to measure the amount of secreting tissue in the kidney.

Although it appeared to us evident that the data as presented had been wrongly interpreted, we appreciated the possibility of correct conclusions in spite of false premises and faulty logic. Consequently, we undertook to secure independent data and to analyze them after their procedure, we sought the aid of Dr. Addis in acquainting us with the detailed records of his experiments reported in summary form. He aided us cheerfully, and his cooperation is hereby gratefully acknowledged.

We deem it important to quote freely and in extenso from the paper of Addis and Foster, not only for clearly demonstrating the steps by which they arrived at their erroneous conclusions, but as well because we find occasion to offer criticism that has general applicability.

Addis and Foster "planned to determine whether there might not be certain special conditions under which the specific gravity of the urine could be used as a means for estimating the amount of secreting tissue in the kidney." They reasoned that "if the specific gravity really does give the concentration of solids in the urine it can be used in conjunction with a determination of the rate of urine excretion to measure the amount of solids excreted per unit of time. This is a measurement which might very well be related to the amount of secreting tissue in the kidney."

* From the Pathological Laboratory and Harriman Research Laboratory, The Roosevelt Hospital

† From the Medical Division, Stanford University Medical School

1 Addis, T., and Foster, Marjorie C. The Specific Gravity of the Urine, Arch. Int. Med. 30 555 (Nov.) 1922

Seeking to induce a demonstration of the maximal concentrating capacity of the kidney, a group of subjects who abstained from fluids for twenty-four hours were put on a constant diet low in fluids, protein and salts. Five experiments were performed on this group of subjects. In each of these, only the night twelve hour samples of urine were collected for analysis. In the first experiment nothing was fed the subjects at the beginning of this twelve hour period. In the other four experiments, specific substances were ingested by the subjects at the beginning of the night period as listed in Table 1. Each sample of urine had quantitative estimations of chlorin, phosphorous and urea in addition to measurements of its volume and specific gravity.

TABLE 1.—Averages from Ten Normal Persons Under Five Different Conditions

Conditions	Specific Gravity	Volume in Cc
Fluid restriction only	1.027	242
Fluid restriction and addition of 30 gm urea in 15 per cent concentration	1.025	597
Fluid restriction and addition of 10 gm sodium chlorid in 5 per cent concentration	1.028	391
Fluid restriction and addition of 10 gm sodium acid phosphate in 5 per cent concentration	1.035	213
Fluid restriction and addition of 30 gm urea, 5 gm sodium chlorid and 5 gm sodium acid phosphate given in 200 c.c. water	1.025	616

Reproduced from paper by Addis and Foster

Continuing with a discussion of Table 1 the authors state:

Contrary to expectation these figures show that the specific gravity of the urine is not greater after the addition of urea, sodium chlorid or a mixture of urea, chloride and phosphate, than after fluid restriction alone. But the main point of interest lies in the fact that the specific gravity results cannot be accounted for fully by the urine volume changes. Their inadequacy can be shown by a consideration of the amount of urea, chlorid and phosphate which were secreted. Thus, in the experiment with simple fluid restrictions the total amount of all three substances was 8.44 gm $(\text{NH}_2)_2\text{CO}$, 5.40 gm $+\text{NaCl}$ 1.78 gm $, +\text{NaH}_2\text{PO}_4$ 1.26 gm). When the mixture was taken the total amount eliminated was 30.19 gm $(\text{NH}_2)_2\text{CO}$, 22.0 gm $, +\text{NaCl}$ 4.63 gm $, +\text{NaH}_2\text{PO}_4$ 3.56 gm). It would be conservative to assume that these three substances together made up more than 75 per cent of the total solids of the urine and the remainder cannot have been far from constant since urines were from the same group of subjects on a fixed diet. The figures 8.44 and 30.19 may be used as an indication of the relative concentration of total solids in the two experiments. In the one case there is 8.44 gm in 242 cc, a 3.48 per cent concentration of solids. In the other, there is 30.19 gm in 616 cc, a 4.90 per cent concentration of solids. If the specific gravity of the urine depended only on the relation between the solids and the water in the urine we should expect to find a higher specific gravity in urine with 4.90 per cent solids than in one with 3.48 per cent solids. But the table shows that the reverse is true, for with 3.48 per cent solids the specific gravity is 1.027 and with 4.90 per cent the specific gravity is 1.025.

The foregoing reasoning is founded on an unwarranted assumption concerning the relationship of total solid weight to the weight of the

specific substances determined by Addis and Foster. It is quite improbable that when a constant diet is the source of a given amount of chlorin, phosphorous and urea, the ratio of the weight of these substances (calculated as sodium chlorid, sodium dihydrogen phosphate and urea) to the weight of the total solids is approximately the same as that obtained after the addition of sodium chlorid, sodium dihydrogen phosphate and urea to this fixed diet. While truly enough the weights of these substances in physiologic urine may represent at least 75 per cent of the total solids as in the first experiment Table 1 (nothing added to diet), they represent at least 95 per cent or more of the total solids in the fifth experiment Table 1 (added salts and urea). This

TABLE 2.—*Results in Experiments 1 and 5*

Name	Volume in C c	Specific Gravity	Urea, Mg per C c	A*			Total Urea, Sodium Chlorid, Dihydrogen Phosphate, Mg per C c	Coefficient †	Ratio ‡
				Sodium Chlorid, Mg per C c	Dihydrogen Phosphate, Mg per C c	Sodium Chlorid, Dihydrogen Phosphate, Mg per C c			
(1) J	205	1.032	35.1	4.68	6.04	45.82	0.143	3.29	
(2) W	330	1.015	14.7	4.85	3.80	23.35	0.156	1.71	
(3) Mc	138	1.029	25.9	11.60	6.05	43.55	0.150	1.47	
(4) S	286	1.029	26.0	10.64	5.67	42.31	0.149	1.59	
(5) U	255	1.025	19.0	11.9	5.95	36.85	0.148	1.07	
(6) B	168	1.036	25.7	8.56	8.45	42.71	0.119	1.51	
(7) K	165	1.034	35.6	8.63	7.50	51.73	0.133	2.21	
(8) Sh	393	1.014	14.05	2.85	2.95	19.85	0.142	2.42	
B§									
(1) J	575	1.029	40.0	8.63	6.55	55.18	0.191	2.65	
(2) W	577	1.023	37.0	11.65	4.50	53.15	0.231	2.30	
(3) Mc	677	1.020	31.5	4.50	4.68	40.68	0.204	3.46	
(4) S	648	1.026	32.7	8.78	5.26	46.74	0.180	2.33	
(5) U	587	1.031	38.2	10.3	5.91	54.41	0.175	2.37	
(6) B	565	1.025	37.0	4.40	6.26	47.66	0.190	3.49	
(7) K	670	1.029	33.5	8.84	5.80	48.14	0.143	2.29	
(8) Sl	675	1.021	36.5	3.79	4.59	44.88	0.214	4.4	
(9) Bo	637	1.024	34.2	7.28	5.40	46.88	0.195	2.69	

* Columns 1 through 5 contain the extensive data on which the summary of Experiment 1 (fluid restricted only), Table 1 is based. For convenience, we have expressed as milligrams per cubic centimeter the concentration of the specific compounds. In the original data percentile expressions were used. Columns 6, 7 and 8 are added by us as based on data in Columns 1 through 5.

† Column 6 divided by last three figures of the specific gravity.

‡ Column 3 divided by the sum of Columns 4 and 5.

§ Columns 1 through 5 contain the complete data on which the summary of Experiment 5 (added urea, sodium chlorid and phosphate), Table 1 is based.

is clearly brought out by the analysis of the figures in Column 7, Table 2. The coefficients given therein are secured by dividing the weight per cubic centimeter of the substances estimated by the last three figures of the specific gravity. For any given specific gravity the greater the weight of the solids, the greater numerically the coefficient. In Experiment 1, Table 1 (restricted fluids only), the average coefficient is 0.143. In Experiment 5, Table 1 (added salts and urea), the average coefficient is 0.191. Coefficients based on estimations of total solids have been between 0.23 and 0.26.² The coefficients supplied by urine samples of

Experiment 5 more closely approach those derived from estimations of total solids. The ratio of the coefficients of the two experiments—1 and 5—give an approximate measure of the proportion of the total solid weight the specific substances determined by Addis and Foster represent in each of the experiments. Taking the coefficient of Experiment 5, Table 1 (added salts and urea), as unity, that of Experiment 1 is 0.75.

The authors continue, then, discussion of Table 1.

The explanation of this apparent paradox lies in the fact—known ever since the first specific gravity was measured—that each dissolved substance has its own specific effect on the specific gravity of a solution. This fundamental fact is generally ignored in discussions on the specific gravity of the urine and either tacitly or openly, it is assumed that the specific gravity measures the total concentration of solids.

Some rough determinations of the specific gravity of varying concentrations of urea, sodium chloride and sodium dihydrogen phosphate are given in the accompanying figure.

Then follows a graph depicting the fact that in pure solution sodium chloride and sodium dihydrogen phosphate for a given concentration induce a considerably higher specific gravity than does urea. A 1 per cent sodium chloride solution has about the same specific gravity as a 2.5 per cent urea solution.

The assumption that the specific gravity measures the total concentration of solids is more thoroughly grounded in fact than the authors' assumption that it does not. They ignore the work of Trapp, Haeser, Naubauer and Long.² The authors are much concerned about total solids, but confine their knowledge of the total solids of specimens in their experiment to assumptions—assumptions which, as explained above, led to erroneous deductions.

Now follows Addis and Foster's explanation of the "apparent paradox."

This graph shows how it came about that the specific gravity of the urine was lower after taking a mixture of urea, chloride and phosphate than after simple water restriction, even though the total concentration of solids was greater. It was lower because a greater proportion of the total solids consisted of urea which has less effect in raising the specific gravity than chlorides or phosphates.

Within the range of temperatures at which the specific gravity of urine is usually taken, a 2.5 per cent urea solution in water gives about the same specific gravity as a 1 per cent solution of a mixture of sodium chloride and sodium dihydrogen phosphate (within the limits of proportions of these two salts as found in urine). Therefore, if the ratio of the concentration of urea to sodium chloride plus sodium dihydrogen phosphate in a sample of urine was greater than 2.5, the tendency ought to be toward a relatively lower specific gravity, if this

explanation of the paradox is correct. In Column 8, Table 2, are given these ratios for each sample of urine. We see at once that the explanation of the paradox is refuted by an apparently new paradox. That not only do samples (comparing urines of the same subject in both experiments) with relatively greater concentration of salts as against urea give lower specific gravities, but a lower specific gravity is secured in a specimen with a higher concentration of all three compounds.

Thus a sample of urine of subject J, Experiment 5 (Table 2 B) has a specific gravity of 1.029 as against 1.032 in Experiment 1 (Table 2 A), even though the concentration of urea and salts in the former is higher. In fact, five of the eight subjects of the experiments supply samples of urine in which the higher specific gravity is of a sample with the relatively greater concentration of urea.

Table 1 summarizes the data from eight to ten subjects by expressing each of the three functions concerned, that is, concentrations of salts and urea, volume and specific gravity as a simple arithmetical average of each function taken alone. This is not at all permissible. It in no way gives the data of the specimen the term "average" seeks to picture—the specific gravity, volume and weight of specific substances in a composite urine of the sample secreted by all subjects at the same hours following a constant diet. The only way we know of actually obtaining such data is by mixing the total volumes or a given aliquot of the urines of all the subjects, taking a specific gravity reading and estimating the weights of the substances concerned.

It is not our purpose to discuss here the statistical methods for determining relationships. We need only emphasize the fact that Table 1 is a false summary of Table 2, on the data of which Table 1 is based. Eight specimens are hardly enough for statistical treatment. More important than the expression of a central tendency as given by an "average" is the measure of the deviation from that tendency—variability. If measures of the variability of the "average" of the three functions studied were included in Table 1, the unreliability of the average would be seen at a glance.

To what absurdities poor statistical handling may lead is seen in the following taken from Table 1:

Specific gravity 1.027 of a "Urine" with $\begin{cases} 2.23\% \text{ urea} \\ 0.736\% \text{ chlorid} \\ 0.520\% \text{ phosphate} \end{cases}$
and a

Specific gravity 1.025 of a "Urine" with $\begin{cases} 3.57\% \text{ urea} \\ 0.751\% \text{ chlorid} \\ 0.578\% \text{ phosphate} \end{cases}$

While the salt concentration is practically identical in both "samples," the urine having 14 per cent more urea has the lower specific

gravity This would make it appear that one could add urea to urine and thereby depress the specific gravity This cannot be done

The explanation of the apparent paradox induced by Addis and Foster is quite apparent Measuring a portion of the urinary solids in two experiments they wrongly assumed that those measures bore the same relationship to the total solids of the urines of their experiments, and therefore drew conclusions concerning total solids and specific gravity The difficulty was further complicated by the improper use of the arithmetical average in summarizing their data

The number of specimens secured were too few to prove anything, and in all events, the conditions of the experiment made it impossible to conclude anything concerning the total solids of the urine

In Table 3 are given seventy-one records of urine from the same person The patient was on a fairly constant diet throughout the period of observation The samples represent two hour specimens passed during the day and from eight to twelve hour samples of the night Collections of samples extended over a consecutive period of more than a week The specific gravities were taken at room temperature The determination of the specific gravities was made by the drop method, employing Dr William G Exton's³ immiscible balance which offers a satisfactory and accurate procedure The coefficients in the last column of the table were estimated to enable one to draw some conclusions concerning the adequacy of the method here used for studying the relationship of total solids to specific gravity in urine The mean of the coefficients is 0.1356 with an average deviation of 0.0118, which is 8.7 per cent of the mean An analysis of the coefficients in Long's² records (fifty-two cases) of his study of total solids shows the average deviation to be only 4.1 per cent of the mean And where, seeking to study only the products of metabolism, he attempted to allow for the effects of the sodium chlorid, he found that the average deviation from the mean was greater⁴

A study of the relationship between the specific gravity and the total solids in urine demands estimations of total solids and not merely of certain constituents of the urine Although the correlation of specific gravity measures and total solid concentration is not perfect—not the most unimportant reason for this may be limitations in accuracy for the recording and determination of these measures—it is strongly positive For clinical purposes the specific gravity may serve as an excellent measure of total solid concentration

³ Exton, W G Trans Am Urological Assn **12** 83, 1920

⁴ Long, J H J Am Chem Soc **25** 871 (Aug) 1903

TABLE 3—Seventy-One Records of Urine from Same Person

Specific Gravity	Urea, Mg per C c	Sodium Chlorid, Mg per C c	Sodium Dihydrogen Phosphate, Mg per C c	Total Urea, Sodium Chlorid and Sodium Dihydrogen Phosphate, Mg per C c	Coefficient*
1	1.0065	4.22	3.2	0.22	7.64
2	1.010	4.89	5.2	0.11	10.20
3	1.0205	17.1	9.6	0.50	27.20
4	1.0195	15.3	9.6	1.51	26.41
5	1.0285	33.0	4.4	4.72	42.12
6†	1.020	16.5	7.2	2.11	25.81
7†	1.0225	18.8	9.5	2.31	30.61
8†	1.0205	18.7	8.7	2.15	29.55
9	1.0135	11.2	6.5	0.99	18.69
10	1.0125	8.83	6.4	0.55	15.78
11	1.0095	5.25	5.1	0.22	10.57
12	1.014	9.22	6.9	1.16	17.28
13	1.025	31.2	1.6	4.30	37.1
14	1.030	34.9	1.5	4.57	40.97
15	1.0265	30.4	3.8	4.27	38.47
16	1.017	14.9	7.0	1.47	23.37
17	1.012	7.5	6.2	0.163	13.86
18	1.0195	12.7	9.6	0.59	22.89
19	1.0205	13.1	9.6	0.69	23.39
20	1.0285	26.5	9.6	3.33	39.43
21	1.0305	28.3	9.0	4.23	41.53
22	1.030	27.4	9.6	3.41	40.41
23	1.0225	20.6	9.0	3.51	33.11
24	1.0305	27.1	8.9	4.84	40.84
25	1.0285	24.6	9.7	4.11	38.41
26	1.021	20.5	7.2	1.51	29.21
27	1.032	35.8	5.0	4.62	45.42
28	1.019	13.3	9.7	1.16	24.16
29	1.0125	9.7	5.6	0.38	15.68
30	1.012	7.5	7.9	0.19	15.59
31	1.020	15.8	9.6	1.63	27.03
32	1.0325	40.4	5.8	3.84	50.04
33	1.033	41.2	6.4	3.76	52.36
34	1.030	30.9	8.0	4.49	43.39
35	1.0335	39.5	8.0	4.18	51.68
36	1.026	21.7	9.6	1.28	32.58
37	1.018	14.0	9.4	0.81	24.21
38	1.023	19.0	9.8	1.12	29.92
39	1.0225	20.3	9.6	0.74	30.64
40	1.025	25.0	9.8	2.71	37.51
41	1.0315	35.2	9.4	4.34	48.94
42	1.033	40.5	7.4	4.68	52.58
43	1.032	38.2	6.2	4.57	48.97
44	1.026	23.9	9.8	2.13	35.83
45	1.0255	25.5	9.8	1.47	36.77
46	1.020	15.7	9.6	0.81	26.11
47	1.026	28.0	7.2	2.83	38.03
48	1.038	47.8	8.6	3.99	61.39
49	1.0305	30.0	7.5	4.07	41.57
50	1.0265	28.4	9.7	3.14	41.24
51	1.0265	27.1	9.8	2.85	39.75
52	1.0095	8.84	2.2	1.12	12.16
53	1.023	22.5	9.8	1.98	34.28
54	1.0095	6.93	5.6	0.70	13.23
55	1.0095	7.50	2.2	3.29	12.99
56	1.018	16.2	7.0	2.25	25.45
57	1.022	21.7	9.7	1.71	33.11
58	1.012	8.73	4.9	0.93	14.56
59	1.0125	9.12	4.5	0.97	14.59
60	1.0175	13.7	9.7	0.54	24.94
61	1.0165	14.7	6.8	1.70	23.2
62	1.018	14.3	9.6	0.81	24.71
63	1.009	4.5	4.4	0.66	9.56
64	1.020	16.5	9.6	2.36	28.46
65	1.0225	20.3	9.6	2.48	32.38
66	1.0095	5.98	4.2	0.58	10.76
67	1.013	9.75	3.4	1.12	14.27
68	1.0135	9.93	5.6	1.18	16.71
69	1.010	6.14	5.0	0.85	11.99
70	1.0125	9.98	4.4	1.16	15.54
71	1.009	6.93	2.8	0.66	10.39

* Secured by dividing Column 5 by the last three figures of the specific gravity.

† Twenty-four (24) hour specimen.

COMMENTS

By DR THOMAS ADDIS

Dr Sharlit and Dr Lyle read more in the paper by Miss Foster and myself than is actually there. They apparently suppose that our data led us to conclude that the specific gravity of the urine can never be used to obtain even an approximate idea of the total solids of the urine. There is, of course, nothing in our experiments which has any bearing on Long's conclusion that the total solids may be estimated within a certain limit of error from the specific gravity under the particular conditions of his experiments. What we did conclude was that the total solids could not be even approximately measured from the specific gravity under the particular conditions of our experiments, these conditions being as far removed as possible from those observed by Long.

The error in the estimation of total solids from the specific gravity varies directly with changes in the relative proportions of the various urinary constituents. In normal persons under ordinary dietetic conditions it has been shown that the changes in the relative proportions of urea, chlorids, phosphates and other substances in the urine are not so pronounced as to introduce a large error. But it surely requires no labored statistical proof to allow the conclusion to be drawn that the use of any such coefficient as Long's will not give even an approximate idea of the total solid content of the urine when the usual relation between the proportions of urinary constituents in the urine has been completely destroyed by increasing the proportion of either urea, chlorid or phosphate. Under such conditions, a statistical proof is superfluous because the conclusion is a deduction from the elementary fact that equal amounts of urea and sodium chlorid have the same effect on the total solid content but have a very diverse effect on the specific gravity. As Dr Sharlit and Dr Lyle, referring to our work, say, "the conditions of the experiment made it impossible to conclude anything concerning the total solids of the urine." That is exactly what our experiments were designed to show, that is, that there are conditions under which the specific gravity must necessarily give an entirely erroneous idea as to the total solid content.

If total solid estimations based on specific gravity measurements were to be used in cases of chronic nephritis, there would be uncertainty as to whether under these pathologic conditions there might not be changes in the relative proportions of the various urinary constituents which would lead to serious error. For this reason alone we felt justified in concluding that "specific gravity determinations cannot form part of any method intended to measure the amount of secreting tissue in the kidney." But even if it were found that the total solids could be fairly accurately determined from the specific

gravity, the results would be as useless for estimating the mass of functioning renal tissue as are determinations of nitrogen, chlorid, or any other urinary constituent. Only the ratio between the total urinary constituents in the blood and in the urine could be expected to measure the amount of renal tissue. But when it is remembered what extreme variations in the relative concentrations of urea and of chlorid occur in the blood when most of the kidney substance has been destroyed by disease, it is clear that specific gravity determinations could not be used. The urea concentration may increase to ten, twenty, or thirty times its normal value, while the chlorid concentration shows no appreciable change or tends to fall.

It may very well be that Long's coefficient may have certain uses in clinical work, but under the special conditions of our experiments, and for the particular quantitative purposes we were discussing in our paper, it is quite clearly inapplicable.

COMPARISON OF CONSTANTS FOR THE DETERMINATION OF VITAL CAPACITY

WILLIS S LEMON, M B (Tor)

AND

HERMAN J MOERSCH, M D

ROCHESTER, MINN

Since 1917 there has been a general revival of interest in the study of vital capacity, as first brought forth by Hutchinson,¹ of England, in 1846. This renewed interest is primarily due to the thorough work of Peabody and Wentworth,² of this country, and Dreyer,³ of England. The literature on the subject since 1917 has become extensive, both from the clinical and investigative aspect, and has been chiefly concerned with the determination of what the normal capacity should be for a given person. Many methods have been advocated as being best suited for the determination of the standard capacity, and there are almost as many different formulas as authors on the subject. Hutchinson attempted to show that the standard vital capacity varied directly with the height of the person. More recently Peabody and Wentworth have studied the problem of vital capacity, and have classified persons into groups according to their height. Bohr⁴ was the first to object to the establishment of the standard based on height alone, and later Dreyer in an extensive and careful study demonstrated that the standard vital capacity varied according to the body surface more closely than with any other body measurement. West⁵ and others have confirmed these observations.

1 Hutchinson, J. Von der Kapazität der Lungen und von den Athmungs-Functionen mit Hinblick auf die Begründung einer genauen und leichten Methode Krankheiten der Lungen durch das Spirometer zu entdecken, Braunschweig, F Vieweg und Sohn, 1849

2 Peabody, F W, and Wentworth, J A Clinical Studies of the Respiration IV The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch Int Med **20** 443-467, 1917

3 Dreyer, G. The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the Body, New York, Paul B Hoeber, 1921. Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **197** 227-234, 1919. Dreyer, G., and Burrell L S T. The Vital Capacity Constants Applied to the Study of Pulmonary Tuberculosis, Lancet **198** 1212-1216, 1920

4 Bohr, C. Die funktionellen Aenderungen in der Mittellage und Vitalkapazität der Lungen, Deutsch Arch f klin Med **88** 382-434, 1917

5 West, H F. Clinical Studies on Respiration A Comparison of Various Standards for Normal Vital Capacity of the Lungs, Arch Int Med **25** 306-316, 1920

Because of the multiplicity of formulas and methods, it was thought that a comparison of the results obtained by using the various methods on the same group of subjects would be advantageous. It was hoped that such a comparison might lead to the selection of some one method that was accurate, and at the same time simple enough for general routine use. With this purpose in mind, 165 men and 166 women were selected for study from the preoperative surgical group of the Mayo Clinic. All patients suffering from pulmonary and cardiac conditions, or from inanition, were excluded. The diagnoses of the conditions of those selected include lipoma, hernia, and various conditions unassociated with asthenia or cachexia. Such a selection affords a varied, but generally uncomplicated, type of condition, and thus serves to determine the applicability of the various methods. These subjects were patients such as would ordinarily be encountered by the physician or surgeon in

TABLE 1.—*Physical Measurements in Male Subjects Used for Vital Capacity Tests*

	Cases	Age, Years	Height, Cm	Weight, Kg	Vital Capacity, Cc	Surface Area, Sq M	Circum- ference of Chest, Cm
Schuster (Oxford)	959		176.5	68.5	4,315	1.83	
West (Harvard)	85		173.5	64.5	4,651	1.78	
Hewlett and Jackson (Stanford) (Arch Int Med 513, 1922)	29						
Hutchinson (England)	400	18 to 30	175.9	68.5	4,646	1.84	
Dreyer (England)	1,285		171.5	68.3	3,602	1.80	
Mayo Clinic	16	13 to 52			4,140		86.6
	165	19 to 70	171.5	69.0	4,487	1.80	89.8

his practice. As every formula was applied to each person examined in the group, the methods were subjected to the same variations, and it is, therefore, possible to determine the value of each from a comparison of the results.

The patients examined came from all parts of the United States and Canada, from the Arctic circle to Texas, and from the Atlantic to the Pacific seaboard. The majority, however, came from the middle western states and western Canada. This is of interest because the results reported by various authors would seem to indicate a variation in the normal vital capacity for people from various countries, or even from different sections of the same country (Tables 1 and 2). Our figures can be considered as a fairly representative average of the whole country, although the number of determinations is too few to form a premise for conclusive argument.

Dreyer demonstrated that the vital capacity varied for training, sex, and certain occupations, a fact that is too often overlooked, and is left out of account in practically all other methods. In our series, many occupations are listed, and the ages vary from 14 to 70 years, therefore

comprising a fairly representative group. Familiarity with the procedure and the cooperation of the patient influence the results in measuring vital capacity, and must be considered before drawing conclusions as to what is the normal vital capacity of a given person. Pratt's observation is of great interest "Furthermore, the vital capacity test of the same person may vary from time to time. I have recorded the amount of variation of the vital capacity in nine persons with apparently healthy hearts and lungs, over periods ranging from fourteen months to three years and four months. Although the seven men in the group were urged to make a maximal exertion at each test, and they apparently did so, the variation was considerable, ranging from 100 to 550 cc. In the period covered by these tests there was no decrease that could be attributed to increasing age." In this regard, it is of interest to speculate on the possibilities of the influence of light, temperature, atmospheric pressure, water vapor, extraneous stimuli and food ingestion on vital capacity determinations, both from a physiologic

TABLE 2—*Physical Measurements in Female Subjects Used for Vital Capacity Tests*

	Cases	Age, Years	Height, Cm	Weight, Kg	Vital Capacity, Cc	Surface Area, Sq M	Circum- ference of Chest, Cm
West (Harvard)	44				3,338		
Myers	94	20 to 30	161.8	57.3	2,992	1.60	
Peabody and Wentworth					3,050		
Mayo Clinic	166	14 to 66	160.7	61.6	3,061	1.62	77.9

and a technical standpoint Haldane,⁶ Krogh,⁷ Lindhard,⁸ Hasselbalch⁹ and others¹⁰ have demonstrated the influence of these factors on the gaseous interchange in the lungs and external respiration. Vital capacity is nothing more than a part of this intricate mechanism.

The spirometer used in our work was of the wet type, and especially constructed for our use by Mr Little of the Mayo Clinic (Fig 1). By means of this instrument, it is possible to determine the amount of air expired within 8 cc. It is so delicately balanced that the slightest inspiration on the part of the patient is observed on the scale. A spring cock valve at the opening into the tank permits closure of the intake, or outlet, of air at any point in the respiratory cycle. The mouth piece

6 Haldane, J S Some Recent Advances in the Physiology of Respiration, Renal Secretion and Circulation, Brit M J 1 409-413, 1921

7 Krogh, A, in Abderhalden, E Handbuch der biochemischen Arbeitsmethoden, Berlin, Urban and Schwarzenberg, 1915

8 Lindhard, J The Seasonal Periodicity in Respiration, Skand Arch f Physiol 26 221-314, 1912

9 Hasselbalch, K A, quoted by Haldane Footnote 6

10 Hoover, C F The Respiratory Significance of Moisture in the Air Spaces of the Lungs, Med Rec 93 1008, 1918

of the instrument is of nickel, may be easily and rapidly sterilized, and is so constructed that it can be firmly held in the mouth without permitting leakage.

All readings were taken with the person in the standing position, with all clothing removed from the chest, except a cape in the case

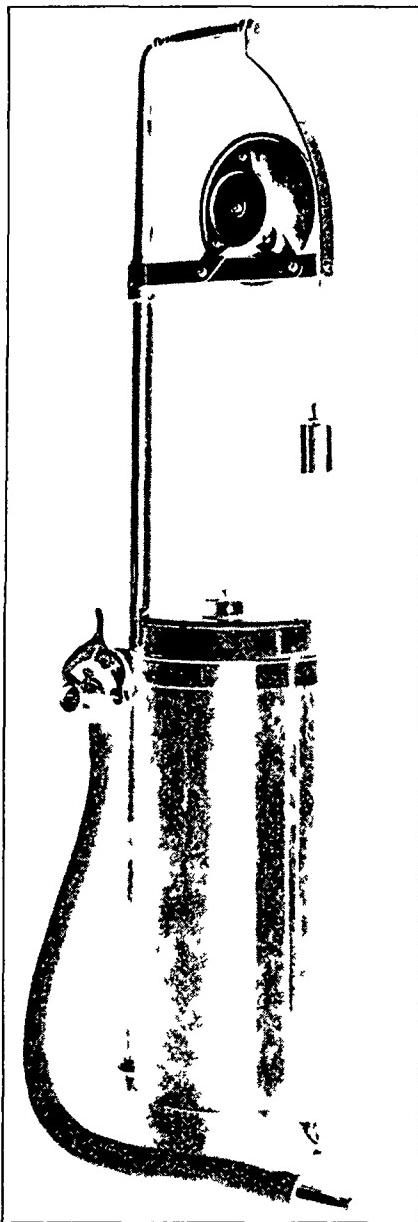


Fig 1.—Spirometer used in work reported

of women. The subjects were instructed to take the deepest possible inspiration and expiration, keep the nose closed, expiring at a fairly uniform rate, and preventing any possible escape of air about the mouth piece. We did not use a nasal clip because patients frequently complained that it annoyed them. We believe we obtained better results from closure of the nares by thumb and finger pressure. Leakage

about the mouth piece was easily determined, as the nickle became fogged if air escaped from about it

All physical measurements were made in the nude, and in accordance with the instructions of the various authors, in the case of women, allowance was made for a sheet and cape, although the tape was applied next to the skin. To obtain the greatest accuracy, readings should be taken at the same time of day, in a room that is of uniform temperature, and on patients who have been protected against fatigue. From three to five, and even more determinations were made in each instance, the highest being accepted. Several patients cooperated so poorly that their readings had to be discarded, and if there was any suspicion of questionable endeavor, this was likewise done. An interesting observation was made in the following instance. A group of six men were examined individually, and the readings noted. Then all six were admitted to the same room at the same time, and a contest instituted to see who could get the highest reading. All but one increased his previous readings by several hundred cubic centimeters.

In order to compare the physique of our subjects with that of subjects examined elsewhere, the various measurements were tabulated (Table 1).

The deviation of weight from normal is not included in the table, because our normals were established from the table used on Toledo scales, and we were unable to ascertain the standards used by other observers. The average deviation for our subjects was 7.5 per cent, while that given by other observers was from 7.3 to 8.8 per cent.

From Table 1 it may be seen that our averages compare favorably with those of others, although our group is not so highly selected as in the other series represented. Thirty-two of our subjects were somewhat overweight (average 5.6 per cent), and 122 were below weight (average 8 per cent). The latter, however, in many instances had higher vital capacity readings than their calculated normal.

In Table 2, similar observations on females are compared with those of Myers,¹¹ West, Peabody and Wentworth. Here again it may be seen that our unselected series compares favorably with Myer's selected series. With regard to variation in weight, it was found that forty subjects were overweight, averaging 8.5 per cent, and 104 were underweight, with a percentage variation of 10.8 per cent. Like the men, these women had higher capacities than their calculated normals.

11 Myers, J A. A Study of the Vital Capacity and Physical Fitness of Nurses, with Tables Showing Calculated Vital Capacities for Normal Men and Women and a Method for Quickly Obtaining an Expression of an Individual Physical Fitness, *Journal-Lancet* 41: 252-257, 1921.

CHART FOR BODY SURFACE DETERMINATIONS

WM BOOTHBY RBSANDIFORD
SEPTEMBER 1920

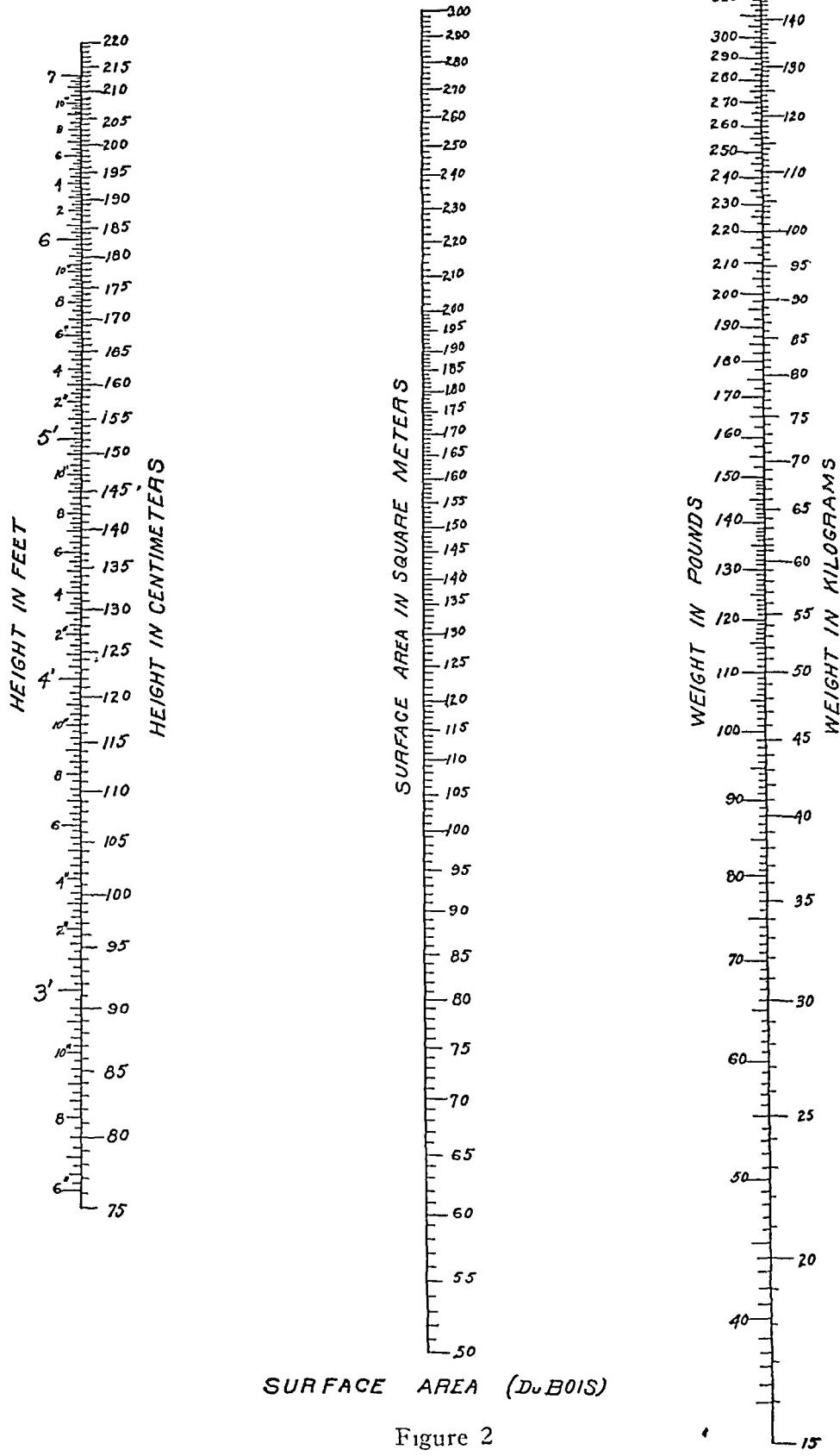


Figure 2

We were desious of knowing whether the constants advocated by us when using the vaious formulas (seven in all) were approximately those of the authors themselves, or of other observers employing them. A comparison of the constants may be seen in Table 3. In Table 3, it will be seen that constant K1 in the male is practically identical with that obtained by Dreyer and by Schuster,¹² whereas it is greater than that of West. From Table 1 it will be noted that this may be in part accounted for by the larger vital capacity readings in West's series, while the weight averages are lower. This is in agreement with the findings of West himself, as he found that the K1 is 0.591 in case of athletes, in whom we have increased vital capacities without a proportional increase in the weight. The remainder of the constants, with the exception of that obtained by means of Lundsgaard and Van Slyke's

TABLE 3—*A Comparison of Our Constants with Those of Others Obtained by the Various Formulas*

	K 1	K 2	K 3	K 4	K 5	K 6	K 7
	W 0.72 V C	W 2/3 V C	Ch 2 V C	V C W	V O H	V O B S	100 × V C Chest Vol
Observations on Men							
Schuster	0.690		1.82				
West	0.632	0.350			26.5	2.61	63.0
Dreyer	0.690	0.457	1.84				
Peabody					26.3		
Lundsgaard and Van Slyke							45.0
Mayo Clinic	0.698		1.88	0.067	26.1	2.49	41.4
Observations on Women							
West	0.807				20.6	2.07	
Myers	0.892					1.87	
Mayo Clinic	0.936		2.11	0.051	18.8	1.87	46.5

Slyke's¹³ formula, are in fairly close agreement. In case of the latter formula, our findings force us to agree with West that when this constant is used, too large a percentage of the people have vital capacity estimations above normal. In the females, the variations are greater than in the males, but unfortunately, the amount of work carried out on females does not approximate that for males. In our series, 166 women were examined as against ninety-four in Myers', and forty-four in West's. The two constants that Myers has applied to his series, however, are in fairly close agreement with ours. The greater discrepancy in the female is due probably to the greater difficulty in taking body measurements, the unfamiliarity of the subjects with the technic of forceful expiration, lack of physical development and unwillingness to cooperate to the extreme of their ability.

12 Schuster, E. First Results from the Oxford Anthropometric Laboratory, *Biometrika* 8:40, 1911.

13 Lundsgaard, C., and Van Slyke, D. Relation Between Thorax Size and Lung Volume in Normal Adults, *J Exper Med* 27:65-85, 1918.

We next tabulated the vital capacity readings according to the height divisions formulated by Peabody, and our results compare favorably with those obtained by him (Table 4). While the averages of the different series are fairly close, with the exception of the males in Group 1, there is much to be said against this method. As has been frequently pointed out, it discriminates against the person whose height comes on the borderline between two classes. This discrimination is especially important if one assumes that a variation of more than 10 per cent below the calculated vital capacity is pathologic. In spite of this discrepancy, the general results compare fairly favorably with those of other methods, as will be seen later.

For comparative purposes, we next calculated the vital capacity of each subject, by each of the various formulas advocated, and the averages obtained are tabulated in Table 5, against the average of the

TABLE 4.—*Spirometer Readings*

	Height			
	Group 1		Group 2	
	155.5 Cm and Up	Vital Capacity, C c	173.3 to 182.5 Cm	Vital Capacity, C c
Men				Group 3
Peabody and Wentworth	5,100		4,800	4,000
Mayo Clinic	5,450		4,885	4,205
Height				
	Group 1	Group 2	Group 3	Group 4
	167 Cm and Up,	162 to 167 Cm,	154.5 to 162 Cm,	Below 154.5 Cm,
	Vital Capacity, C c			
Women				
Peabody and Wentworth	3,275	3,050	2,825	
Myers	3,260	2,970	2,973	
Mayo Clinic	3,371	3,156	3,003	2,857
				2,834

observed vital capacities for our subjects, as well as the average percentage variation of each from the average observed vital capacity.

In summarizing the tables, it is found that, in the case of males, the vital capacity calculated by means of West's formula (body surface in square meters times 2,500) gives the closest agreement with the observed vital capacity of any of the formulas, while the calculation on the basis of height and chest circumference, as well as class, according to Dieyei's method gives almost identical results. Dieyei originally, in creating his formula, used the stem length of the individual rather than the height, however, we used the height rather than the stem length because of the difficulty attached to measuring the stem length, especially in old persons.

In the case of females, West's formula (height in centimeters times 20) expressed the calculated vital capacity in the closest agreement with the observed vital capacity of any of the formulas. West's body surface formula (body surface times 2,000) comes next in order. Peabody and Wentworth's method for calculating the vital capacity

TABLE 5.—*Series of Cases Used as Basis of Comparison for Various Methods for Estimating Vital Capacity*

Formulas	Males						Females						Mean Difference Between Calculated and Observed Vital Capacity When Observed Was the Greater, Cc	Mean Difference Between Calculated and Observed Vital Capacity When Observed Was the Lower than Observed, Cc	Grand Average Where Calculated Vital Capacity Varied from Observed, per Cent for Each Person
	Cases with Calculated Vital Capacity Higher than Observed	Average Vital Capacity Calculated Where It Was Higher than Observed	Average Calculated Vital Capacity	Cases with Calculated Vital Capacity Higher than Observed, per Cent	Average Vital Capacity Calculated Where It Was Lower than Observed	Cases with Calculated Vital Capacity Lower than Observed, per Cent	Average Vital Capacity Calculated Where It Was Lower than Observed	Cases with Calculated Vital Capacity Lower than Observed, per Cent	Average Vital Capacity Calculated Where It Was Lower than Observed	Cases with Calculated Vital Capacity Lower than Observed, per Cent	Average Vital Capacity Calculated Where It Was Lower than Observed	Cases with Calculated Vital Capacity Lower than Observed, per Cent			
Body surface in sq meters times 2.5	74	4,004	630	14.11	90	4,428	481	10.86	12.27						
liters (West)	58	4,228	515	12.18	106	4,316	612	14.17	13.46						
Height, cm times 2.5 (West)															
W 0.72	62	4,708	787	16.71	102	4,212	509	14.22	15.15						
<u>0.630</u> (Dreyer)															
*Oh 2 (Dreyer)	64	5,015	1,108	22.09	99	4,925	620	14.67	17.58						
1.82															
*Vital capacity from weight (Dreyer's book)	48	4,532	697	15.38	115	4,126	651	15.77	15.65						
*Height and circumference of chest (Dreyer)	64	4,424	526	11.88	96	4,368	519	12.36	12.28						
*Standard of heights (Peribody and Wentworth)	65	4,363	523	11.98	97	4,352	575	13.21	12.71						
21.2 times body weight plus 1,68 (Myers)	59	4,690	786	16.75	105	4,207	611	14.52	15.32						
Weight in gm times 0.066	72	5,057	974	19.26	92	4,147	656	15.81	17.32						
Body surface in sq meters times 2	110	3,306	469	14.18	56	3,170	289	9.11	*	12.46					
liters (West)	107	3,215	442	13.74	50	3,224	295	9.12	12.09						
Height, cm times 20 (West)															
Standard of height (Peribody and Wentworth)	68	2,928	329	11.23	98	2,940	402	13.07	12.66						
17.6 times body weight plus 900 (Myers)	105	3,474	600	17.27	61	2,969	365	12.29	15.43						
<u>W 0.73</u> (Dreyer)	124	3,635	725	19.94	42	3,093	334	10.79	17.62						
Vital capacity from weight (Dreyer's book)	100	3,420	535	15.59	63	2,904	361	12.43	14.33						
Height and circumference of chest (Dreyer)	103	3,370	521	15.46	48	3,117	302	9.68	13.62						

* We are unable to obtain complete figures for 164 persons because the original authors' standards were not extensive enough to include all variations in height, chest circumference and so forth.

based on various height standards ranks third, for the smallest percentage variation from the observed vital capacity for both males and females.

From our series, it would, therefore, seem that West's formula (body surface in square meters times 2,500 in the case of men, and 2,000 in case of women) expresses the calculated vital capacity more accurately than any of the other methods, while West's formula (height in centimeters times 25 in case of men and times 20 in case of women) and Peabody and Wentworth's method are next in order. The Dreyer formula based on height and chest circumference is found to be less accurate for the female, owing to the difficulty in making chest measurements.

Objection may be raised to the use of body surface method of calculating vital capacity because of the difficulty in calculating the body surface. However, this difficulty is easily overcome by use of the chart constructed by Boothby and Sandiford for the determination of the surface area by the DuBois formula (Fig. 2). By means of this chart, all that is necessary is to connect the height and weight on the respective outside lines by means of a straight edge or rule, and read off the figures for body surface area where it bisects the middle line.

CONCLUSION

It seems to us that West's formula (body surface in square meters times a constant, 2,500 in case of men, and 2,000 in case of women) expresses the calculated vital capacity the most accurately and simply of any of the foregoing methods.

VITAL CAPACITY IN RELATION TO OPERATIVE RISK

WILLIS S LEMON, M.B. (Tor.)

AND

HERMAN J MOERSCH, M.D.

ROCHESTER, MINN

The question of operative risk is one of great interest as well as concern to the surgeon, and justly deserves his consideration. At the present time, he must estimate the operative risk from the patient's general condition, age, obesity and blood pressure, from the type of lesion and from his own skill and experience. While these factors may at times furnish the basis for an accurate estimation of the risk, they often involve danger to the less experienced surgeon, and at times even to the most skilled, on account of their variability and the difficulty of interpretation. Various conditions, such as nasal and bronchial infections, and the like, may lie dormant and give no indication of their presence until the patient's resistance has been lowered sufficiently by operation to permit exacerbation. It is often impossible to anticipate such complications even from the most careful history.

In view of the fairly accurate estimation which vital capacity gives of a person's physical fitness, it seemed plausible that operative risk might be estimated by the same method. We, therefore, took vital capacity determinations on 379 consecutive patients before operation, and checked the findings against the final outcome of the operation, as well as against the surgeon's own estimate of the operative risk, based on the patient's general condition. The risk for each patient was estimated on the basis of four, and the risk was calculated from the vital capacity determinations as follows:

TABLE 1.—*Risk Calculated from Vital Capacity Determinations*

Risk	Vital Capacity, per Cent
1	—10 to normal
2	—20 to 10
3	—30 to 20
4	—30 and below

Of the 379 patients examined, twenty-three did not come to operation. The operative risk for the group of twenty-three, as calculated from the vital capacity determinations, was as follows: risk 1, fifteen; risk 2, four; risk 3, two; and risk 4, two. Two of the twenty-three

patients died while in the hospital under observation. For these patients, the operative risk as determined from the vital capacity determinations was 3 in one instance and 4 in the other, the surgeon in both instances estimated the risk at 4.

Nine (2.53 per cent) of the 356 patients who came to operation died. The operative risks, as determined from the vital capacity findings for the nine fatal cases, are given in Table 2, and compared with the risk as estimated by the surgeon.

TABLE 2.—*Operative Risk in Nine Cases*

Degree of Operative Risk	Risk as Calculated from Vital Capacity, Cases	Operative Risk Calculated by Surgeon, Cases
1	3	2
2	3	5
3	2	1
4	1	1

Of the patients with an uneventful recovery, the risks as estimated from the vital capacity findings were as follows: risk 1, 233; risk 2, fifty-three; risk 3, thirty-six; and risk 4, twenty-five.

It was found that the surgeon considered the operative risk higher in seventy-two instances than the vital capacity determinations indicated, whereas the reverse was true in thirty-two instances. Several factors account for this variation. The operative risk calculated from the vital capacity was based simply on the patient's physical fitness. On the other hand, the surgeon had the benefit of his own knowledge of the type of disease and of his skill in performing the particular operation under consideration, and also of the internist's opinion regarding the patient's general condition. None of these factors was included in the calculation from the vital capacity readings.

For routine purposes, the determination of the operative risk from the surgeon's opinion is probably, on the whole, a more satisfactory estimate than that obtained by means of the vital capacity readings. However, if the surgeon does not have the benefit of experience, or the assistance of an experienced internist in making such an estimate, especially in questionable cardiac and pulmonary conditions, vital capacity determinations may be of the greatest aid. From whatever cause, the closer the approximation of vital capacity to tidal air, the graver will the risk become. When low readings are obtained, the surgeon would do well to institute preoperative measures, and to make further observations before attempting operation.

BASAL METABOLISM AND VITAL CAPACITY

WILLIS S LEMON, M.B. (Tor.)

AND

HERMAN J MOERSCH, M.D.

ROCHESTER, MINN

It is often observed that patients affected by exophthalmic goiter have a decreased vital capacity, and in taking the vital capacity of a number of such patients we noted that in several instances patients with the high basal metabolic rates had a relatively lower vital capacity than those with low metabolic rates. These observations prompted investigation to determine whether there is any fixed relationship between basal metabolism and vital capacity, and whether the thyroid secretion which causes the variations in metabolic rates likewise has an indirect compensatory action causing parallel fluctuations in the vital capacity. If this should be true, there would be at our disposal an easy method for determining thyroid activity.

With this purpose in mind, eighty-five subjects with goiter were examined. The diagnosis as to the type of goiter in each instance was based on the clinical findings, basal metabolic rates and postoperative histologic diagnosis in the majority of instances. The series was made up of twelve males and forty-six females with exophthalmic goiter, five males and twenty females with adenoma of the thyroid, two patients with thyroiditis, as well as with myxedema, and one with anorrhexia nervosa. Such a series was selected because of the wide range in basal metabolic rates it afforded.

The vital capacities were all taken with a wet type of spirometer, and a technic described by us in an earlier publication. In each instance the estimated normal vital capacity was calculated according to the following methods: (1) height in centimeters times 25 for males and times 20 for females (West¹), (2) body surface in square meters times 2,500 for males and times 2,000 for females (West), and (3) from tables given in Dreyer's² "The Assessment of Physical Fitness." All three methods were used in order to obviate so far as possible

¹ West, H F Clinical Studies on Respiration A Comparison of Various Standards for Normal Vital Capacity of the Lungs, Arch Int Med 25 306-316 (March) 1920

² Dreyer, G The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the body, New York, Paul B Hoeber, 1921

errors that might occur through sudden changes in weight which so often occur in cases of exophthalmic goiter. The basal metabolic readings were all made in Dr. Boothby's laboratory at the Mayo Clinic, the open circuit type of gasometer being employed.

Repeated vital capacity and basal metabolic determinations were made on as many of the subjects as possible, in order to determine whether variations in the basal metabolic rate of the same person were accompanied by vital capacity changes. At first, similar determinations were made immediately following thyroidectomy, but these were discontinued on account of the poor cooperation of the patients because of their fear of causing a postoperative injury. In calculating the estimated normal vital capacity for the subjects, various factors, such as physical fitness, type of employment, training, age and sex were also taken into consideration.

TABLE 1.—*Observations on Relationship Between Basal Metabolic Rate and Vital Capacity in Fifty-Eight Patients with Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism*

Basal Metabolic Rate	Number of Cases	Vital Capacity Variation from Normal, as Calculated from West's Body Surface Formula, per Cent
0 to + 20	1	-26
+20 to + 30	7	-7 4 to -35 9
+30 to + 40	12	+ 0 2 to -39 2
+40 to + 50	14	+ 0 6 to -74 3
+50 to + 60	7	+18 2 to -44 8
+60 to + 70	9	-8 6 to -32 6
+70 to + 80	3	+ 0 4 to -19 4
+80 to +102	5	-27 2 to -32 4

On tabulating the basal metabolic and vital capacity findings it was found that although in the largest percentage of instances there was a tendency toward decreased vital capacity with increased metabolic rates, especially in cases of exophthalmic goiter, no definite relationship between the two was evident. A patient with a basal metabolic rate of + 17 per cent may have just as great a decrease in vital capacity as one with a rate of + 70 per cent (Table 1).

In a study of twenty-five patients with adenoma of the thyroid without hyperthyroidism, a similar inconstancy between basal metabolic rate and vital capacity was found to exist.

It was further noted that many of the patients with decreased vital capacity and increased metabolic rates had an increase of vital capacity and a decrease in basal metabolism after rest. That this was not dependent alone on the change in basal metabolic rate was evident from the fact that while, in most instances, the rate fell somewhat in those patients whose vital capacity increased on rest, it did not always fall. An increase in vital capacity can occur without lowering of the basal rate (Cases 7 and 14, Table 2), and a decrease in basal metabolic rate

on rest is not always associated with an increase in the vital capacity (Cases 3, 5 and 9, Table 2)

When the basal metabolic rate fell, an increase in vital capacity usually appeared but without any constancy. No rule could be applied to anticipate the changes that appeared.

It is true, however, on the whole, that the subjects with the greater decrease in vital capacity had an increase following rest, while less change was noted in those with smaller variations from normal.

It was found that the subjects with a decrease in vital capacity in most instances also had some cardiac decompensation, and that as the vital capacity decreased, the degree of cardiac decompensation became more marked. In almost every instance, it was found that it was the patients with the cardiac decompensation whose vital capacity

TABLE 2—*Changes in Vital Capacity with Changes in Basal Metabolic Rate*

Case	Vital Capacity	Basal Metabolic Rate	Interval in Days Between Readings	Vital Capacity	Basal Metabolic Rate
1	2,302	+ .25	7	2,893	+ .7
2	2,667	+ .25	12	2,659	+ .40
3	2,832	+ .28	13	2,867	+ .14
4	3,102	+ .36	13	3,406	+ .28
5	3,632	+ .45	8	3,328	+ .30
6	2,066	+ .56	13	1,963	+ .47
7	1,998	+ .61	13	2,181	+ .62
8	1,859	+ .62	12	1,920	+ .53
9	2,615	+ .63	7	2,607	+ .47
10	3,336	+ .63	7	3,415	+ .45
11	2,259	+ .64	12	2,711	+ .33
12	2,589	+ .70	13	2,580	+ .78
13	2,242	+ .81	7	2,433	+ .66
14	2,328	+102	12	2,867	+108

increased with rest. Those who did not register an improvement in vital capacity had no decompensation, or being decompensated, gave no evidence of improvement. We, therefore, attempted to find the relationship that might exist between the degree of cardiac decompensation and vital capacity.

The patients were divided into five groups, according to the amount of decompensation, the first group being normal. As no definite measurable factor was available for estimating the decompensation, it had to be based on clinical manifestations, history and electrocardiograms. Dyspnea was of special value in making these calculations, as has been demonstrated by Peabody and Wentworth,³ who found that a fairly reliable opinion as to the cardiac efficiency can be obtained from this symptom. The results obtained by this classification are given in Table 3.

³ Peabody, F. W., and Wentworth, J. A. Clinical Studies of the Respiration IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch Int Med 20: 443-467 (Sept.) 1917.

It is seen from Table 3 that a relationship exists between cardiac compensation and vital capacity. Peabody and Wentworth, in 1907, divided a group of patients with cardiac disease into four groups on the basis of the vital capacity findings those with a vital capacity of not more than — 10 per cent of normal as Group 1, — 10 to — 30 per cent as Group 2, — 30 to — 60 per cent as Group 3, and below that as Group 4. In Group 1 there existed little or no cardiac decompensation and no dyspnea, while in each succeeding group these findings became more marked. In our series we classified the patients according to symptoms. Group 1 represented those having slight dyspnea and initial signs of cardiac inefficiency, while in each succeeding group the disability became more urgent. While differences exist between the two series, our findings tend to take the same course as those of Peabody and Wentworth.

TABLE 3.—Relationship Between Cardiac Efficiency and Vital Capacity in Cases of Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism (Cardiac Efficiency Classified on Basis of Scale of 4)

Cardiac Efficiency	Number of Cases	Percentage of Vital Capacity Variation from Calculated Normal		
		West's Body Surface Formula	West's Height Formula	Dreyer's Height and Chest Circumference Method
Normal	11	—16.7	—17.4	—13.6
—I	19	—15.4	—16.7	—16.7
—II	16	—24.4	—29.9	—26.9
—III	11	—32.6	—34.4	—35.6
—IV	1	—74.3	—67.8	—70.1
Adenoma without Hyperthyroidism				
Normal	17	—1.5	—5.7	+1.8
—I	4	—11.7	—7.9	—7.4
—II	3	—28.6	—18.2	—23.4
—III				
—IV	1	—44.6	—41.0	—44.9

A division of the same series on the basis of edema alone likewise gave a similar indication of the deviation of the vital capacity from normal, as might be expected. The subjects were divided into groups on the basis of four, and the figures obtained are given in Table 4. As in the preceding classification, the basis of division is rather inaccurate, as it depends on individual interpretation of the classifying factor. From Table 4 it will be seen that in the higher grades of edema there was a diminution of the vital capacity, and that in a way the results are parallel to those obtained from the study of cardiac decompensation.

One is often impressed with the observation that persons vary in their response to thyroid secretion. In one person a moderate elevation in basal metabolism is accompanied by marked symptoms, while in another with the same, or even higher, rate only a few symptoms of hyperthyroidism exist. The vital capacity findings were therefore charted according to the severity of the symptoms to determine whether

this might show any relationship, but no constant relationship was found, although there was a tendency on the whole toward decreased vital capacity in those with the most marked symptoms (Table 5).

Exophthalmos and crisis likewise was of little value. In the former, no relationship between the degree of exophthalmos and vital capacity

TABLE 4.—Relationship Between Degree of Edema (Erythema) and Vital Capacity in Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism (Edema Classified on the Scale of 4)

Fdem ¹	Number of Cases	Percentage of Vital Capacity Variation from Calculated Normal		
		West's Body Surface Formula	West's Height Formula	Dreyer's Height and Chest Circumference Method
0	28	-19.2	-23.3	-19.2
I	18	-20.5	-20.5	-21.3
II	10	-32.5	-36.1	-31.6
III	2	-37.2	-33.5	-38.7
Adenoma of Thyroid without Hyperthyroidism				
0	23	-11.5	-11.5	-7.1
I	2	-4.9	+1.2	+19.0

TABLE 5.—Relationship Between Severity of Symptoms and Vital Capacity in Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism (Severity of Symptoms Classified on Scale of 4)

Severity of Symptoms	Number of Cases	Percentage of Vital Capacity Variation from Calculated Normal		
		West's Body Surface Formula	West's Height Formula	Dreyer's Height and Chest Circumference Method
I	14	-17.5	-19.7	-18.9
II	23	-19.1	-24.1	-20.7
III	11	-27.2	-32.1	-32.8
IV	9	-33.5	-29.1	-22.6

TABLE 6.—Relationship Between Duration of Symptoms and Vital Capacity in Exophthalmic Goiter and Adenoma of the Thyroid with Hyperthyroidism

Duration of Symptoms	Number of Cases	Percentage of Vital Capacity Variation from Calculated Normal		
		West's Body Surface Formula	West's Height Formula	Dreyer's Height and Chest Circumference Method
½ year or less	15	-28.9	-32.0	-28.2
½ to 1 year	14	-19.4	-24.9	-17.2
1 to 1½ years	6	-14.1	-15.2	-18.1
1½ to 2 years	6	-17.1	-19.7	-16.7
2 to 3 years	2	-29.1	-27.6	-24.8
3 to 5 years	3	-18.0	-20.1	-14.6
5 to 10 years	4	-26.8	-29.1	-31.0

was anticipated, while in the latter we cannot say just what the relationship would be during the crisis, as the number of determinations has been too small, but between crises evidence of such a relationship is lacking. Family history likewise bears no relationship to the matter.

Due to the increased activity of the heart in hyperthyroidism, one might anticipate in time a gradual decrease in cardiac efficiency, provided

this increased activity along with any toxicity that may exist has an injurious effect on the heart. In order to determine whether such a condition existed, the vital capacity variations were grouped as to duration of symptoms into periods of six months each, and the results for exophthalmic goiter patients in our series are tabulated in Table 6.

While the number of determinations is really too small to permit the drawing of definite conclusions, it would seem that one cannot predict accurately the decrease in vital capacity that can be anticipated from the duration of the disease.

It was of interest to note that in all instances the women gave on the whole greater variations in the vital capacity findings than did the men. This is in agreement with the observations made in an earlier paper.

The findings on the two patients with thyroiditis examined followed the same general trend as those with exophthalmic goiter. In the patient with myxedema and the one with anorexia nervosa, each of whom had a decreased metabolic rate but a normal heart, the same relationship was found to exist. In fact, the anorexia nervosa patient, in spite of his loss of strength and weight, had an increased vital capacity.

As to the primary fundamental physicochemical cause of the decreased vital capacity in hyperthyroidism, we are still uncertain and must await further investigation. However, we believe the secondary and direct cause is the cardiac inefficiency which arises from the primary source, the thyroid.

FACTORS INFLUENCING VITAL CAPACITY

WILLIS S LEMON, M B (Tor)
AND
HERMAN J MOERSCH, M D
ROCHESTER, MINN

Various considerations regarding vital capacity, as observed in a study of 225 men and 238 women at the Mayo Clinic, have already been presented. It became apparent that certain more general factors were repeated with such constancy that they must be considered in the interpretation of all estimations. Our observations regarding the relative importance of these factors are reported here.

SEX

It was anticipated that the vital capacity of the women of our series would be less than that of the men. We found in our group, which comprises the types of patients usually seen in ordinary practice, that the formula of West¹ was more suitable because of the ease of estimation and exactness. This formula takes into consideration the body surface measurements and a constant that varies with sex. Such constants as were proposed by West agreed with our findings, and we believe are best used when developing normals for comparison with actual spirometer readings. The factor of sex is not accidental or infrequently found, but seems to have a constant influence. West is not alone in making allowance for sex in estimating capacity. In our group, adults alone were studied, but a variation also obtains between boys and girls, as was shown by Stewart and Sheets,² who studied the vital capacities of 430 children. They found that boys always gave higher readings than girls. Menstruation may have some effect on the capacity of women, but we have no determinations to prove the supposition, and have found none in the literature.

Wittich, Myers, and Jennings,³ however, have found that pregnancy has no influence on the readings, and cannot be a factor in its interpretation. Although their group is small, their conclusions are well supported. We did not make observations on pregnant patients.

1 West, H F Clinical Studies on Respiration A Comparison of Various Standards for Normal Vital Capacity of the Lungs, Arch Int Med **25** 306-316 (March) 1920

2 Stewart, C A, and Sheets, O B Vital Capacity of Lungs of Children, Am J Dis Child **24** 83-88 (July) 1922

3 Wittich, F W, Myers, J A, and Jennings, F L A Study of the Effect of Pulmonary Tuberculosis on Vital Capacity, J A M A **75** 1249-1252 (Nov 6) 1920

PHYSICAL FITNESS

Physical fitness is so important a factor that we wish to recall particularly the work of Dreyer⁴ in England, and of Hewlett and Jackson⁵ in this country. Dreyer found it desirable to classify all people of the same stature into three groups on the basis of their physical fitness: (1) those active in athletics, military training, or vigorous outdoor labor were classified in Group 1, (2 and 3) those occupied in tasks less arduous or less conducive to physical development. He found that persons in Group 1 had higher vital capacity values than those in Group 2 or 3. This observation is important in estimating vital capacity, especially when readings become pathologic. We found that we could not disregard the individual fitness, for it became apparent that the readings for an athlete might be normal from the point of view of stature, and irrespective of training, but lower than normal for a man of his training. The reverse, however, is true of the person of poor physical training, who may have a vital capacity normal for himself, but so low as to be pathologic if compared with that of an athlete. The truth of these observations has been noted in all the selected groups studied, and has been particularly well demonstrated when young college athletes have been the subjects of observation.

AGE

Age, which plays such an important part in most bodily functions, does not seem to influence the vital capacity of adults to any marked degree before 50 or 60 years of age. Even after this period of life its effect is variable, and the decrease in vital capacity is generally found to run parallel with the change in general bodily turgor and elasticity, and to accompany the decrease in physical fitness which usually occurs at this period of life. In men in the seventies, the vital capacity readings may be normal, or even above normal. Unfortunately, the number of persons over 50 and 60 years of age studied are relatively few compared to the number studied before this period of life. In the table we have tabulated from the readings of 165 men and 165 women from our group the vital capacity for each decade and for each group on the basis of physical fitness. A small decrease in vital capacity is observed as the decades progress, but age plays an indefinite rôle. The degenerative changes which appear in man with advancing years, and the changes in height and weight provide many reasons for such a decrease and are factors of such changing character and often so

⁴ Dreyer, G. The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the Body. New York, Paul B. Hoeber, 1921. Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, *Lancet* 2: 227-234, 1919.

⁵ Hewlett, A. W. and Jackson, U. R. The Vital Capacity in a Group of College Students, *Arch. Int. Med.* 29: 513-526 (April) 1922.

difficult to determine that they are equally difficult to evaluate in making estimations. A rather marked difference appears in the groups arranged from the estimated physical fitness. Our findings agree with those of Dreyer, Peabody and Wentworth, and of Hutchinson⁶ in a study of 1,775 subjects. Hutchinson found a definite decrease in vital capacity after 50 years of age. Pratt,⁷ in a study of ninety cases, obtained results somewhat similar to those of Hutchinson, although there was apparently little variation in vital capacity until after 60 years of age. One factor which both Hutchinson and Pratt failed to take into consideration in classifying their results is physical fitness. This in part accounts for the apparently greater decrease in vital capacity after 50 years of age as compared with our series.

Relationship Between Age and Vital Capacity Classified on the Basis of Physical Fitness

Age, Years	Group 1		Male		Group 3	
	Cases	Average Vital Capacity, C c	Cases	Average Vital Capacity, C c	Cases	Average Vital Capacity, C c
10-20			1	3,910		
20-30	27	5,013	8	4,170	1	4,519
30-40	27	4,556	13	4,249		
40-50	22	4,827	24	4,204	1	2,685
50-60	17	4,765	10	3,813		
60-80	5	4,033	8	4,064		
Female						
10-20			2	1,963		
20-30	4	2,987	29	3,150	1	3,371
30-40	5	3,248	37	3,107	6	2,945
40-50	4	3,740	41	3,147	3	3,116
50-60	2	3,115	20	2,773	4	2,494
60-80			5	2,697	2	1,851

BODILY MEASUREMENTS

Hutchinson, the first worker to undertake the study of vital capacity, noted that a relationship existed between vital capacity and various bodily measurements. He believed that it was probably a function of height rather than of any other measurement. Since that time it has been noted that a relationship exists between vital capacity and other bodily measurements, such as weight, stem length, chest circumference, chest capacity and body surface. Dreyer, in 1919, investigated the relationship between these various factors, with the exception of chest capacity, and came to the conclusion that vital capacity was more nearly a function of body surface than of any other bodily measurement. This was later corroborated by West, who also considered the relationship between chest volume and vital capacity. In an earlier paper on the

6 Hutchinson, J. Von der Kapazität der Lungen und von den Athmungs-Funktionen mit Hinblick auf die Begründung einer genauen und leichten Methode Krankheiten der Lungen durch das Spirometer zu entdecken, Braunschweig, F. Vieweg und Sohn, 1849.

7 Pratt, J. H. Long Continued Observations on the Vital Capacity in Health and Heart Disease, Am J M Sc 164 819-832, 1922.

subject, in which we reviewed the question of the relationship of vital capacity to various bodily measurements as sponsored by various authors, we likewise reached the conclusion that vital capacity is more nearly a function of body surface than of any other bodily measurement.

TEMPERATURE, PULSE AND RESPIRATION

We were interested in discovering whether variations in the fundamental bodily functions of temperature, pulse rate and blood pressure have an influence on vital capacity, or give any indication of its changes. We did not determine the exact influence of temperature on vital capacity because we could not study the effect of high temperatures on a sufficiently large number of persons. However, variations in temperature between 97 and 100 F., as studied in 463 persons without cardiac or pulmonary disease, did not appear to have any definite effect on vital capacity.

Blood pressure alone appears to have little effect on the vital capacity. In an analysis of this group of 463 subjects in which the systolic pressures varied from 80 to 220 mm of mercury, little or no effect was found. The vital capacity varied neither directly nor inversely with the systolic, diastolic or pulse pressures. The pulse rate in persons without cardiac or pulmonary disease gave little indication of the vital capacity. However, if one accepts all cases without regard to physical ailments or deformities, it will be found that there is a tendency toward decreased vital capacity as the pulse rate becomes markedly increased. This is accounted for by the fact that in this group are included patients with exophthalmic goiter and cardiac and pulmonary diseases. A rapid pulse in a person without a complicating cardiac or pulmonary lesion does not indicate a decreased vital capacity, as shown in the chart.

DEFORMITIES OF THE THORAX

Deformities of the thorax deserve an important place in the consideration of vital capacity. Lundsgaard and Van Slyke⁸ were the first to emphasize the relationship between chest volume and vital capacity. They believe that the relationship between the two was closer than between vital capacity and any other bodily measurement. However, Lundsgaard⁹ has recently admitted the possibility of error in determining vital capacity as a percentage of chest volume from the three measurements of the chest, as advocated by Van Slyke and himself, in patients with deformities of the chest and embarrassed

⁸ Lundsgaard, C., and Van Slyke, D. Relation Between Thorax Size and Lung Volume in Normal Adults, *J. Exper. Med.* **27** 65-85, 1918.

⁹ Lundsgaard, C. Determination and Interpretation of Changes in Lung Volumes in Certain Heart Lesions, *J. A. M. A.* **80** 163-167 (Jan 20) 1923.

respiration Peabody and Wentworth¹⁰ first called attention to the fact that flexibility of the thorax influenced the vital capacity. This is readily understood when one remembers that the thoracic cavity is enlarged by movement of the diaphragm and of the sternum and ribs upward, as well as the ribs laterally. The lungs can only fill with air to the extent which the thoracic cavity permits. In this connection one must consider ossification of the costovertebral joints, cartilage, etc., as possible influencing factors operating through a decrease of the flexibility of the thoracic frame. It was our good fortune to examine a man with ossification and fixation of the costovertebral joints, causing a complete immobilization of the thorax. The vital capacity was found

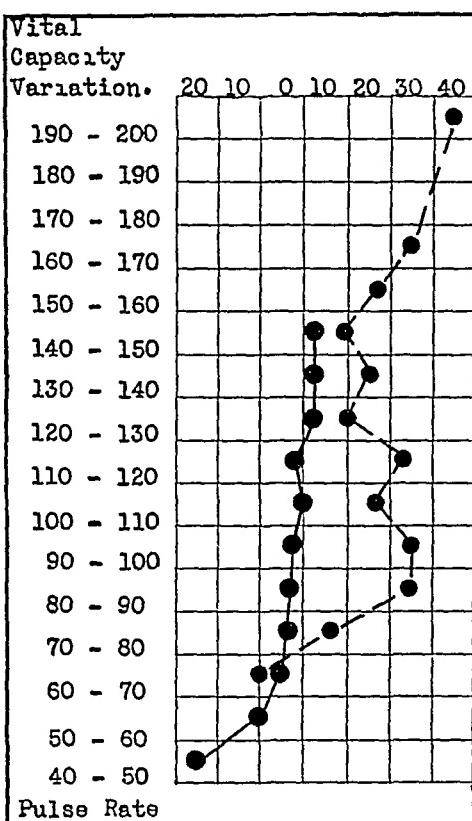


Chart 1.—Relationship between pulse rate and vital capacity in conditions with and without cardiac complications. The broken line indicates the pulse rate in conditions with cardiac complications (51), the solid line in conditions without cardiac complications (295).

10 Peabody, F W, and Wentworth, J A Clinical Studies of the Respiration IV The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch Int Med **20** 443-467 (Sept) 1917 Peabody, F W, Wentworth, J A, and Barker, Bertha Clinical Studies on Respiration The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, Arch Int Med **20** 468-478 (Sept) 1917 Peabody, F Clinical Studies on the Respiration The Acidosis of Chronic Nephritis, Arch Int Med **16** 955-966 (Dec) 1915, Clinical Studies on the Respiration The Effect of Carbon Dioxide in the Inspired Air on Patients with Cardiac Disease, *ibid* **16** 846-864 (Nov) 1915

reduced as anticipated. The calculated vital capacity according to West's body surface formula was 4,800 cc while the observed vital capacity was 3,258 cc, or 32.1 per cent below normal. Strange to say, the patient was capable of participating in a game of ball or hockey without the least discomfort or dyspnea. Normal standards, estimated by any method, are subject to error in such persons, and ability to function without embarrassment is the best evidence of sufficient vital capacity.

MUSCULAR DEVELOPMENT

Peabody and Sturgis¹¹ found in cardiac cases that general muscular weakness and fatigue of the muscles of respiration are not important factors in causing a reduction of the vital capacity. In contradistinction to this conclusion, Levine and Wilson¹² conclude from a study of persons with irritable heart that fatigue results in the reduction of vital capacity. This conclusion they base chiefly on the observation that a greater decrease occurs after exercise than before, as compared with the results in normal persons. They found, however, that the small decrease in vital capacity in patients with irritable heart is not sufficient to account for the dyspnea that exists. It would seem to us that a weakening of the muscles of respiration could and should be a factor in causing a decrease in vital capacity. We often observe in conditions in which a portion of the respiratory musculature is incapacitated that decrease in vital capacity coexists, and that this decrease is proportionate to the importance and extent of the respiratory muscles involved. This was well demonstrated by a patient with chronic poliomyelitis who came under our observation. The intercostal muscles were paralyzed, the left side of the diaphragm was found to move only a little, and the right side about one half of its normal excursion, as observed under the fluoroscope. So far as we were able to determine, there existed no gross cardiac or pulmonary disease. This patient's vital capacity was found to be 1,510 cc, or 65.4 per cent of the normal as calculated from West's body surface formula. Although fatigue does not have as marked an effect on the respiratory muscles as was found in the foregoing example, it does have an effect. How great an effect we have been unable to determine.

ABDOMINAL PRESSURE

The effect of variations of intra-abdominal pressure on vital capacity is uncertain. It would seem probable that any condition in the abdomen that interfered with free movements of the diaphragm would influence it. However, in many such cases, pain, as well as

¹¹ Peabody, F. W., and Sturgis, C. C. Clinical Studies of the Respiration. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs, Arch. Int. Med. 28: 501-510 (Nov.) 1921.

¹² Levine, S. A., and Wilson, F. N. Observations on the Vital Capacity of the Lungs in Cases of Irritable Heart, Heart 7: 53-61, 1918-1919.

complicating cardiac and pulmonary conditions, coexist, which make the results questionable. The observation of Wittich, Myers and Jennings that pregnancy influences vital capacity very little is of importance. Equally important is the observation of Lewis that abdominal pressure in animals under deep anesthesia plays no part in the production of respiratory curves. In our series, vital capacities taken on seven women suffering with large fibroids or cystic ovaries showed variations in vital capacity from + 92 per cent to - 28 per cent of the calculated normal, while in one man with a large abdominal tumor, due to a large hydronephrotic sac, the variation was - 13 per cent of the calculated normal.

PLEURAL AND PULMONARY CHANGES

It is understood and easily demonstrated that anything which impinges on the pleural cavity and causes a decrease in lung volume from retraction or displacement of the lung tissue will also cause a decrease in vital capacity, depending on the amount of tissue affected, and the degree of interference with respiratory excursion or interference with the passage of air into other portions of the lungs. This reduction is found in cases of pleural effusion, pneumothorax, tumors of the chest wall, pleura and the mediastinum. Pleural adhesions which prevent the proper excursion of the lung must likewise be considered, as they cause a decrease in vital capacity, as demonstrated by Myers.¹³ It is equally well known that anything which interferes with the admission or egress of air from the lungs will decrease vital capacity. The more marked the condition and the longer it interferes with the free passage of air, the more marked will be the reduction. Myers found in bronchial asthma, in which the free passage of air to and from the alveoli is impeded, that during the attack there is a decrease of as much as 18 to 20 per cent in the vital capacity, which returns to normal after the attack, providing no complications exist or arise.

Dreyer and Burrell¹⁴ and others have very well demonstrated the relationship that was found to exist between the extent of tuberculosis and the decrease in vital capacity, which is common in this disease.

13 Myers, J A. Respiratory Organs in Health and Disease, Correlation of Symptoms, Vital Capacity Readings and Physical and X-Ray Findings in 619 Cases Examined for Pulmonary Tuberculosis, Am Rev Tuberc 6 702-706, 1922, Respiratory Organs in Health and Disease, Significance of Vital Capacity Test in Pulmonary Tuberculosis, Bronchial Asthma, Pneumonia, and Acute Infection Outside Respiratory Tract, Arch Int Med 30 648-667 (Nov) 1922, A Study of Vital Capacity and Physical Fitness of Nurses, with Tables Showing Calculated Vital Capacities for Normal Men and Women and a Method for Quickly Obtaining an Expression of an Individual's Physical Fitness, Journal-Lancet 41 252-257, 1921.

14 Dreyer, G., and Burrell, L S T. Vital Capacity Constants Applied to the Study of Pulmonary Tuberculosis, Lancet 1 1212-1216, 1920, 2 374-376, 1922.

Siebeck¹⁵ believes that this decrease in vital capacity in tuberculosis is due to an increase of the residual air volume, a decrease in the elasticity of the lung tissue and less forceful expiration. We have found that pneumonia, pleural effusions, bronchiectasis, emphysema, lung abscess, primary and secondary pulmonary growths and a large variety of less common diseases influence the vital capacity. The degree of reduction is an important prognostic consideration in all conditions when surgical intervention is indicated. The nearer the vital capacity approaches the tidal air, the graver will be the risk of operation.

CARDIAC CONDITIONS

Variations in cardiac efficiency are found to exercise a marked influence on vital capacity. Peabody and Wentworth, in 1918 in a thorough review of the question, demonstrated that, in cardiac conditions, the vital capacity varied with the cardiac efficiency. Opitz¹⁶ further demonstrated that cardiac disease without decompensation does not influence vital capacity. These findings have been corroborated by other investigators dealing with the question. Our findings relative to the question of the relationship between cardiac efficiency and vital capacity have been reviewed previously, and will not be dealt with here. Cardiac condition should, however, be included in the list of known factors influencing the determination of the vital capacity.

HYPERTHYROIDISM

It is often noted that in hyperthyroidism, vital capacity is decreased. In a previous article, this entire problem was reviewed, and it was found that the vital capacity was proportional to the cardiac efficiency and bore no constant relationship to the degree of toxicity.

EXTRANEous INFLUENCES

There are various extraneous influences that must be considered in making vital capacity determinations. The question as to the most favorable position in which to place a person while making the determination must be considered, especially if one accepts the dictum that vital capacities 10 per cent below the calculated normal are pathologic. A great deal of uncertainty still exists as to which position is best. Christie and Beams¹⁷ found that the vital capacity taken in a reclining position averaged 5.5 per cent below that taken in the sitting position.

¹⁵ Siebeck, R. Ueber die Beeinflussung der Atemmechanik durch krankhafte Zustände des Respiration—und Kreislaufapparates, Deutsch Arch f klin Med **100** 204-220, 1910.

¹⁶ Opitz, R. Vital Capacity of "Cardiacs," J A M A **78** 1686-1687 (June 3) 1922.

¹⁷ Christie, C., and Beams, A. J. Estimation of Normal Vital Capacity, with Especial Reference to Effect of Posture, Arch Int Med **30** 34-39 (July) 1922.

Rubow,¹⁸ and also Hasselbalch¹⁹ found that the vital capacity was greater in the standing than in the sitting position. All our readings were taken with patients standing, and we believe the essential point is that readings be always taken in the same attitude.

Peabody and Wentworth found little variation in vital capacities taken from day to day, while Pratt found that the vital capacity may vary considerably in normal persons over longer periods of time.

It is well to take vital capacities at the same time each day and under as nearly identical conditions as possible. Some patients permit psychic factors to influence them unduly. As we pointed out in a previous paper, patients are often capable of increasing their vital capacity under the stimulus of competition, so that whatever method is originally adopted should be adhered to. The time relationship to meals does not appear to have any influence on vital capacity.

There are undoubtedly various other factors that deserve consideration in vital capacity determinations. Among the more common factors that are generally disregarded are atmospheric pressure, temperature, water vapor, composition of the air, and light and darkness. That atmospheric pressure may have an influence on vital capacity is seen from the observation of Dreyer, who found that continued flying at high altitudes causes a decrease in vital capacity. It is a well-known fact that barometric pressure, temperature and water vapor exert a definite influence on air volume. In just what manner and degree these affect vital capacity is uncertain. Although atmospheric pressure may not influence determinations at any definite locality, when these are compared with similar readings taken in other localities, it may be of importance. Whether these factors account for the difference in the average vital capacity observed in groups of persons of the same training from different countries, is open to discussion. Lindhard,²⁰ in a study of the variations in respiration during various parts of the year in the Arctic circle, found that there was a difference in respiration in the light and dark periods of the year, and believed it was due to action of the light on the respiratory center, similar to the effect of temperature and barometric pressure on the respiratory center, but slower. He postulates that light has some influence on metabolism, therefore causing increased respiration. The purely physical influence of these factors on the air measured and the apparatus used should also be considered.

18 Rubow, V. Untersuchungen über die Atmung bei Herzkrankheiten. Ein Beitrag zum Studium der Pathologie des kleinen Kreislaufes, Deutsch Arch f klin Med **92** 255-281, 1908.

19 Hasselbalch, K A, quoted by Haldane, J S. Some Recent Advances in the Physiology of Respiration, Renal Secretion and Circulation, Brit M J **1** 409-413, 1921.

20 Lindhard, J. The Seasonal Periodicity in Respiration, Skand Arch f Physiol **26** 221-314, 1912.

THE EFFECT OF DYSPNEA VARIOUSLY PRODUCED ON THE VITAL CAPACITY OF THE LUNGS

M JOANNIDES, MD

MINNEAPOLIS

Dyspnea is one of the most constant findings in patients with heart disease. In these cases, Peabody and Wentworth¹ found that there is a diminution in the vital capacity of the lungs, and this diminution varies directly with the degree of dyspnea. These authors, however, attribute this diminution in vital capacity to mechanical factors, such as rigidity of the bony framework of the chest, ankylosis of the costal joints, diminution in the elasticity of the lung tissue, accumulation of fluids in the pleura, enlargement of the heart, enlargement of the liver, etc. These conditions, when present, undoubtedly cause a decrease in the vital capacity of the lungs. There are cases, however, in which such conditions are absent, but still the vital capacity of the lungs is decreased. Peters and Barr² report that the decrease in the vital capacity in heart disease does not depend primarily on anatomic factors, because of the absence of physical signs of congestion or fluid in the thorax, and because of the rapidity with which the vital capacity increases as compensation is established. They give no specific explanation, however, of the cause of this decrease in vital capacity of the lungs. Various types of experiments, therefore, were undertaken in order to find an explanation for this decrease in vital capacity when no mechanical factors are present.

As in the pathologic cases dyspnea and the decrease in vital capacity are usually found together, we felt that by producing dyspnea in persons who are normal and who have a normal vital capacity, we might arrive at some definite conclusion as to the relation of the two phenomena.

METHODS

The methods used in the production of dyspnea were (1) rebreathing air, thereby increasing the carbon dioxide tension of the inspired air, (2) muscular effort such as running, (3) combination of running and rebreathing, (4) breathing air with reduced oxygen tension.

A Krogh³ spirometer of 8 liter capacity was used in most of the experiments. A modification of the Hutchinson⁴ spirometer was used

¹ Peabody, F W, and Wentworth, J A Clinical Studies of the Respiration, IV The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch Int Med 20 443 (Sept) 1917

² Peters and Barr Am J Physiol, December, 1920

³ Krogh Skand Arch f Physiol 27 100, 1912

⁴ Hutchinson Med Chir Trans 29 137 (April 28) 1846

for the study of oxygen diminution in the inspired air. It was found necessary to use rubber tubing with a wide lumen for our connections, because with narrow tubing the subject had to breathe against resistance, a factor which in itself decreases vital capacity. Soda lime was used to absorb the carbon dioxid produced by rebreathing, and thus the effects of anoxemia were studied. In all these experiments a closed circuit was formed between the patient and the apparatus. In order to assure a maximum inspiration, the subject was asked to inspire as deeply as possible, hold his breath for a moment, and make one or two attempts to inspire. Immediately afterwards, he was connected to the spirometer, expired as deeply as possible and finally made one or two further attempts to expire. This method assured a constant reading, especially when single readings were taken.

TABLE I.—*Rebreathing at Tidal Air Amplitudes*

No. of Ex- periment	Total Length of Re- breath- ing in Circuit	Total Air in Sec	Average Vital Capacity in C c		Average Tidal Air in C c		Measured Minute Volume in Liters		Respira- tory Rate per Minute		Fall in Vital Capacity in C c	Rise in Minute Volume in Liters	Final Tidal Air and Vital Capacity, C c	Difference Between Tidal Air and Vital Capacity, C c
			Begin- ning	End	Begin- ning	End	Begin- ning	End	Begin- ning	End				
1	132	8,360	5,160	4,160	1,312	3,520	21 16	55 96	14	16	1,000	34 80	640	
2	109	7,880	5,050	3,976	1,550	3,992	24 80	119 76	16	30	1,104	94 96	-16	
3	102	8,000	4,880	4,770	2,400	3,256	24 00	40 64	10	10	110	16 64	1,514	
4	134	7,920	5,120	4,248	1,016	3,848	12 19	107 92	12	28	872	95 73	409	
5	126	7,600	4,800	4,010	1,336	3,368	16 08	100 32	14	29	760	84 24	672	
6	129	7,300	4,500	3,880	1,168	3,664	16 35	90 48	14	26	620	74 13	216	
7	155	7,264	4,464	4,120	826	3,328	19 52	89 12	14	26	344	69 60	792	
8	120	7,140	4,340	4,048	1,680	3,336	24 60	37 00	14	20	292	12 40	712	
9	420	23,480	4,160	3,760	792	3,334	16 20	93 60	14	28	400	77 40	426	
10	245	24,128	4,808	4,456	360	4,312	14 48	77 04	13	24	352	62 56	496	
11	265	22,820	4,400	4,240	424	2,880	18 00	70 24	15	26	160	52 54	1,600	
12	332	23,108	4,688	3,760	480	2,760	8 64	43 52	18	21	920	34 88	1,000	
13	176	7,824	5,024	3,760	580	2,880	28 48	67 12	24	24	1,264	46 64	880	
14	383	22,920	4,500	3,800	520	1,752	13 92	51 28	21	26	700	37 36	2,048	
15	156	7,344	4,544	3,760	480	1,800	12 80	44 80	21	25	784	32 00	1,960	
16	356	24,300	5,824	5,416	896	2,828	7 75	46 00	9	16	408	38 25	3,088	
17	470	24,200	5,856	4,616	896	2,640	8 96	54 88	10	27	1,240	45 92	1,976	
18	172	8,208	5,408	5,120	928	2,288	24 16	80 88	24	31	288	56 72	2,832	
19	208	7,600	4,800	4,373	1,152	2,587	25 44	109 92	24	43	427	73 48	1,783	

Two types of rebreathing were adopted first, rebreathing with a tidal air amplitude, second, rebreathing with a vital capacity amplitude. When tidal air was used, the mind of the subject was occupied by reading or being spoken to. The tidal air and vital capacity immediately before the experiment were considered as the normals for that time. Rebreathing was continued until the subject could no longer hold out. In several experiments the rebreathing was continued to a point at which nausea and vomiting occurred.

When we speak of vital capacity, we must think of it in terms of the physiologic mechanism involved in exerting a given amount of voluntary effort, so that the maximum amount of air may be inspired or expired. This point of view has been taken into consideration in this work.

In the experiments in which rebreathing was carried out at tidal air amplitudes when marked dyspnea came on, from two to four vital capacity determinations were made. Other factors being equal, the total time of rebreathing depended on the amount of air present in the system at the beginning of the experiment. When the total air ranged between 7,100 and 8,300 cc., the rebreathing interval was from 102 to 208 seconds, and when the air was from 23,000 cc. to 25,000 cc., the rebreathing interval was from 245 to 470 seconds. One, therefore, is justified in assuming that the total duration of rebreathing depends on the rate of change in composition of inspired air, namely, the increase

TABLE 2.—*Prolonged Breathing Against Resistance
Vital Capacity Amplitudes*

Experiment	Total Length in Sec	Respiratory Rate		Average Vital Capacity		Per Second Volume		Pulse Rate per Minute		Fall in Vital Capacity		Remarks
		Beginning	End	Beginning	End	Beginning	End	Beginning	End	Volume in Cc	Per Cent	
		180	10	4,896	4,560	816	760	80	102	336	6.87	
1	330	9	10	4,595	3,856	659	642	80	102	739	16	No dyspnea, sense of fatigue in respiration
2	320	7	12	4,263	3,740	497	748	84	96	523	12.2	No dyspnea, sense of fatigue in respiration
3												Apparent recovery from Experiment 2, no dyspnea, sense of fatigue in intercostal muscles

*Prolonged Breathing at Vital Capacity Amplitude
No Resistance to Breath Against*

Total Length in Seconds	Respiratory Rate per Minute		Average Vital Capacity		Volume in Liters	Minute Volume	Experiment was stopped at will, no dyspnea or fatigue at end of experiment
	Beginning	End	Beginning	End			
	2,732	9	4	4,576	4,496	41.36	18.16

of carbon dioxide tension and decrease of oxygen tension. The point at which extreme dyspnea occurs and the subject is unable to continue rebreathing has been called by Peters and Barr⁵ "the point of intolerance to CO₂." In these experiments, there was a definite but variable decrease in vital capacity. This decrease ranged from 2 to 25.1 per cent of the normal. In general, it was found to be proportional to the degree of dyspnea. The degree of dyspnea was estimated partly on the subjective appearance of the subject and partly on the relative increase in minute volume. The analysis of the following experiments will serve to illustrate the method of making this estimation. In Experiment

5 Peters and Barr Am J Physiol, December, 1920

16 the subject rebreathed until he felt uncomfortable and thought that he could not keep up any longer. At this point he showed only moderate subjective dyspnea and objectively, in spite of the very high initial vital capacity, he had a rather low minute volume, comparatively slow respiratory rate and low tidal air. The result was that at the end of the experiment the final vital capacity was decreased to 5,416 cc. When, however, the same subject was reassured that no ill effects would follow, he repeated the experiment and succeeded in rebreathing for 114 seconds longer. Even though the vital capacity in the beginning varied little, the final vital capacity in this experiment decreased to 4,616 cc, a difference of 800 cc.

TABLE 3.—Rebreathing at Vital Capacity Amplitudes

No. Ex- periment per- mitting ing in Circuit	Total Length in Seconds	Total Air in C c	Respiratory Rate per Minute		Average Vital Capacity in C c		Measured Minute Volume in Liters		Fall in Vital Capacity, in C c		Rise in Minute Volume in Liters	
			Begin- ning	End	Begin- ning	End	Begin- ning	End	in C c	in Liters		
1	100	7,838	8	13	5,088	4,715	40.30	61.30	323	21.00		
2	110	7,647	11	19	4,847	3,912	53.32	74.32	935	21.00		
3	105	7,666	9	18	4,866	4,424	43.80	79.64	442	35.84		
4	120	7,500	8	20	5,000	4,180	40.00	83.60	820	43.60		
5	98	7,836	11	19	5,036	4,398	55.40	83.56	638	28.16		
6	130	7,390	8	12	4,590	3,310	36.72	39.72	1,280	3.00		
7	126	7,180	9	12	4,380	3,847	35.04	46.16	533	11.12		
8	206	25,900	8	11	5,000	4,069	40.00	44.76	931	4.76		
9	128	8,023	7	13	5,223	4,554	36.56	59.20	669	12.64		
10	100	8,147	6	8	5,347	4,550	32.08	36.48	797	4.40		
11	110	8,160	6	12	5,360	4,072	32.16	48.88	1,288	16.72		
12	124	8,093	6	17	5,293	3,972	31.76	67.52	1,321	35.76		
13	103	8,040	5	13	5,240	3,649	26.08	47.44	1,591	21.36		
14	112	7,840	6	15	5,040	3,232	30.24	48.48	1,808	18.24		

Although the rate of respiration is an important factor to be considered, it appears that the decrease in vital capacity in this series is more closely related to the increase in the tidal air amplitude than the rate of respiration. In general, the greater the increase in final tidal air, the greater is the decrease in vital capacity. One may consider the difference between the final tidal air and the final vital capacity as the ultimate voluntary reserve of increase in amplitude of respiration. It is, perhaps, possible to estimate the degree of dyspnea from this difference. Thus, in Experiment 16, in which the dyspnea was only moderate, the difference between the final tidal air and vital capacity is 3,088 cc. On the other hand, in the next experiment, in which the dyspnea was quite marked, this figure dropped to 1,976 cc. In this experiment, even though the vital capacity was decreased by 1,240 cc, and his final tidal air was 2,640 cc, when these figures are compared with those in the sixth experiment, it will be noticed that in the latter, in spite of the relatively small decrease in vital capacity (620 cc) the difference between the final vital capacity and tidal air is as low as 216 cc. That this person was subjected to an extreme dyspnea is also borne out by

the very high minute volume at the end of the experiment, namely 90.48 liters. One is, therefore, justified in concluding from these data that the subject in Experiment 17 had a great deal more reserve and could possibly keep up longer, whereas the subject in Experiment 6 was using his last resources to compensate for the dyspnea.

As the vital capacity determinations depend primarily on voluntary effort, there is a possibility that anticipation of results might produce a decrease in vital capacity. A number of experiments, therefore, were performed on subjects who did not know beforehand what the results would be, and who were willing to cooperate fully with us. These subjects were free from any apparent cardiac or pulmonary disease. The results in these subjects did not differ in any way from those obtained when the experiments were performed on ourselves.

A few experiments were performed with the subject breathing atmospheric air at vital capacity amplitudes, but against resistance. In spite of the absence of any subjective or objective dyspnea, there was a decrease in the vital capacity from 336 c.c. (6.87 per cent) to 739 c.c. (16 per cent). This decrease was undoubtedly the result of fatigue of the muscles of respiration caused by undue effort. Subjectively, voluntary control of these muscles was diminished, and the experiment was terminated on account of discomfort and the cramping of these muscles. That the decrease in vital capacity was not due to breathing per se at vital capacity amplitudes, is evident by the following experiment. Prolonged breathing was carried out at vital capacity amplitudes, and the resistance against breathing was minimized by the use of tubing with a diameter of 22 mm. It was possible to continue the experiment for forty-five and one-half minutes and then stop it at will. The vital capacity ranged within normal variations throughout the experiment. As one would expect, the respiration rate and the minute volume were decreased markedly. No dyspnea or fatigue were experienced subjectively.

In all the experiments in which rebreathing was carried out at vital capacity amplitudes, it was evident that the latter began to diminish gradually from the beginning, slowly at first and then more and more rapidly. The decrease in vital capacity at the end of the experiments ranged between 6.4 per cent and 35.8 per cent of the normal. In this series also, the amount of decrease in vital capacity depends on the degree of dyspnea at the end of the experiment. As the point of intolerance to carbon dioxide approaches, the extent to which rebreathing is continued has a marked effect on the degree and rate of decrease on the vital capacity. If, under such conditions, rebreathing is carried out a few seconds longer, the vital capacity is reduced markedly. The rate of

TABLE 4.—Running Until Hyperventilation Followed by Rebreathing in Untrained Athletes

No of Experi- ment	Total Length of Re- breath- ing	Total Air in Crecnt in Sec	Respiratory Rate per Minute		Vital Capacity in Cc		Tidal Air in Cc		Measured Minute Volume in Liters		Fall in Vital Capacity, in Cc		Rise in Minute Volume in Liters		Remarks
			Begin- ning	End	Begin- ning	End	Begin- ning	End	Begin- ning	End	Begin- ning	End	Begin- ning	End	
1 A	19	34	4,180	3,936	672	1,820	12,768	6240	844	4963	Lifted weight and ran until dyspneic, recovery from increased ventilation				
7 B	19	271	4,750	4,346	672	2,203	12,768	6786	434	5509	Exercise repeated until dyspneic				
1 C	19	233	4,780	4,240	672	2,240	12,768	8711	540	7134	No hypercapnia, apparent recovery from 1 B, exercise (running and lifting weights) continued until dyspnea				
2 A	19	30	5,166	4,293	857	2,980	1636	8940	873	7304	Dyspnea by running down and up stairs of five floors				
2 B	19	38	5,106	4,160	857	2,549	1636	9732	1,006	8096	Continued to run in room after recovery from increased ventilation until dyspneic				
3 A	19	36	4,600	4,300	480	2,915	912	10494	360	9582	Experiment done 6 hours after complete recovery from previous experiment, ran down and up stairs of five floors				
3 B	19	27	4,900	4,350	480	3,120	912	9168	360	8256	Recovery from hyperventilation, run in room until again dyspnea resulted				
3 C	40	7,160	27	30	4,360	3,660	3,120	3,424	9168	9528	700	360	Rebreathing immediately after 3 B at tidal air amplitudes, viral croupy, at beginning 240 c.c. (5%) less than "A"		
3 D	123	22,893	23	26	4,153	4,080	1,424	5180	8362	373	2882	Rebreathing after recovery from 3 C			
4 A	27	5,140	4,773	1,747	897	2,944	36276	8804	867	16764	Ran down and up stairs of five floors, dyspneic immediately after 4, lifting weights until very tired but not dyspneic, unable to go on account of fatigue				
5 A	225	29	5,333	4,860	1,184	1,184	2010	1400	473	2390	Rebreathing immediately after 5 A, no extreme dyspneic, but sense of fatigue and no desire to continue				
6 B	111	33,280	29	32	4,890	4,890	1,184	2,032	4400	65024	60	2103	Rebreathing immediately after 6 A, no extreme dyspneic, but sense of fatigue and no desire to continue		
6 A	20	28	4,740	4,613	784	3,152	1568	8598	127	7030	Ran down and up stairs five floors dyspneic				
6 B	16	36	4,613	4,166	3,152	4,496	9200	10204	507	1064	Ran down and up stairs five floors dyspneic				
7 A	28	36	3,589	2,846	838	2,007	1337	13225	543	11852	Rebreathing immediately after 7 A, tidal air capacity and tidal air are same				
7 B	36	36	2,846	2,233	2,007	2,253	13225	8111	593	593	Fall				

TABLE 5—*Carbon Dioxide Absorbed Reaching at Tidal Air Amplitudes*

No of Experiments	Length of Re-breathing in Sec	Total Air in Circuit in Cc	Average Circuit Capacity in Cc		Average Tidal Air in Cc		Minute Volume in Liters		Respiratory Rate per Minute		Fall in Vital Capacity, Minute Volume in Liters		Remarks
			Beginning	End	Beginning	End	Beginning	End	Beginning	End	15	16	
1	245	8,824	4,129	4,129	1,315	2,093	1973	3349	4115	4115	11	33	No dyspnea, fullness of head, faintness, weakness, poor voluntary control, stopped on account of discomfort
2	268	7,840	3,973	3,746	1,629	1,773	1930	5524	1117	1117	227	3534	Dyspnea, no nervous symptoms
3	258	7,867	4,392	4,060	574	2,285	805	4115	1117	1117	332	3310	No dyspnea, pulsating headache, sense of compression in head, weakness, poor voluntary control
4	295	8,702	3,144	2,289	1,061	1,073	2253	15	21	21	855	661	Dyspnea, no discomfort or dulling
5	117	4,797	4,589	4,086	1,185	1,491	2131	2885	18	18	503	751	No dyspnea, symptoms as in Experiments 1 and 3
6	159	4,917	3,337	2,106	1,090	1,601	1872	1804	18	30	1,231	2932	Dyspnea, cyanosis, some headache or weakness
7	408	8,258	3,516	2,170	787	1,049	1117	2623	18	25	1,346	1206	Pulse, waxy appearance of face, lethargic, eyes half closed, loss of voluntary control
8	243	7,810	4,590	4,134	530	1,005	854	2408	16	15	396	1574	No dyspnea, symptoms same as in Experiments 1 and 3
9	271	5454	3179	2,086	604	1,515	966	2879	16	19	1,003	1913	Dyspnea, some unsteadiness, no cyanosis, no mental symptoms

respiration in this series was quite slow and increased only slightly until the onset of dyspnea. The relative increase in the rate of respiration in both series was approximately the same.

Two types of observations were made in the study of the relation of exercise to vital capacity, and rebreathing immediately after exercise or as soon as the apparent dyspnea disappeared. One set of experiments was performed on athletes at a gymnasium. It was found that ordinary floor exercise did not produce any increased ventilation of the lungs, and therefore did not appreciably change the vital capacity. Running was, therefore, adopted as the exercise of choice for the production of dyspnea. The final determinations were made at the point at which the subject was dyspneic. The apparatus was near at hand so that only a small interval of time elapsed between the end of exercise and the determinations. Nevertheless, some of the athletes so promptly recovered from dyspnea that little or no change in the final vital capacity occurred.

It seemed that prompt recovery in these subjects was due to the fact that they were athletes. Therefore, another set of experiments was carried out on untrained subjects. In most of these subjects the vital capacity was decreased after exercise. The tidal air and minute volumes were increased. Soon after exercise, in spite of the apparent absence of subjective dyspnea the tidal air was somewhat higher than normal, and the vital capacity remained below normal. If rebreathing was carried out at this stage, the interval was diminished by over one half of the rebreathing interval with the same amount of reserve air before exercise. Rebreathing in this series did not change the rate of respiration very much but increased the tidal air considerably. When the minute volume became quite high, it remained close to that level, so that at the beginning of rebreathing it was within the limits of dyspnea. After rebreathing, however, in most cases it rose higher than at the end of exercise.

Rebreathing after exercise is probably analogous to the conditions present in patients with heart disease. These patients, like our normal subjects after exercise, have a vital capacity lower than normal, and can hold their breath for a few seconds after a deep inspiration or a deep expiration, but less than normal. They both have a tendency to dyspnea and a shortened rebreathing interval. In the absence, therefore, of thoracic exudates or transudates or other mechanical conditions to cause an actual diminution in the capacity of the lungs, one is justified to assume that a decrease of the vital capacity of the lungs depends to a great extent on the degree of dyspnea.

The last series of experiments was carried out to determine whether dyspnea produced by conditions other than increase or inspired carbon

dioxide or exercise had the same effect on the vital capacity. In the cases in which there was a decrease in vital capacity, there was subjective dyspnea and objectively an increase in the minute volume. On the other hand, one is not certain of the results in those cases in which the mental symptoms were marked. Thus, in Experiment 7, toward the end the subject was lethargic and practically without any voluntary control over his respirations. In this experiment, therefore, it is difficult to decide whether the decrease in vital capacity is really due to an increased pulmonary ventilation or to a loss of control of his accessory muscles of respiration. In some of the experiments, the discomfort during the experiment was so great that the experiment was terminated before the onset of dyspnea. All attempts in the case of one subject to produce dyspnea were unsuccessful because of the severe sense of compression in the head, and the feeling of having received a blow on the head. The symptoms during this period, and for several hours afterward, were no different than those so well described by J. Barcroft⁶ under the title "Acute Anoxaemia." When one compares the smooth and easy way of producing dyspnea by means of increased inspired carbon dioxide with the discomforting and probably dangerous method with oxygen want, one is justified in discarding the latter method, especially since the changes in the vital capacity cannot be well controlled with the latter method. Moreover, this method was recently tried from the same point of view as in our experiments and was found unsatisfactory by Stengel, Wolferth and Jonas⁷.

SUMMARY

- 1 Dyspnea was produced by the use of exercise, increased carbon dioxide tension in the inspired air and oxygen want.
- 2 When the pulmonary ventilation was increased, there was a decrease in the vital capacity.
- 3 The use of oxygen want for the production of dyspnea does not give well controlled results with reference to the study of vital capacity.
- 4 In a few experiments exercise produced a slight but noticeable increase in vital capacity.
- 5 After exercise, a condition is produced in the body that is quite analogous to that in patients with heart disease with reference to their vital capacity, the tendency to dyspnea and the shortened rebreathing interval.
- 6 The decrease in vital capacity of the lungs is secondary to dyspnea and depends primarily on conditions which produce dyspnea.

⁶ Barcroft, J. Acute Anoxaemia, *Lancet*, September 4, 1920.

⁷ Stengel, Wolferth and Jonas. *Trans Assn Am Physicians*, 1920.

7 Dyspnea, as experimentally produced, always was marked before any appreciable reduction of vital capacity was obtained. It is possible in patients who are physically incapacitated by disease that dyspnea may have a much more marked effect on the vital capacity of the lungs.

8 The reduced vital capacity, in part at least, is presumably due to the dyspnea which enters into the make-up of the clinical picture in patients with cardiac disease.

BOOK REVIEWS

NON-SURGICAL DRAINAGE OF THE GALL TRACT By B B VINCENZI
LYON, A B, MD, Chief of Clinic, Gastro-Intestinal Department of the Jefferson Medical College, Attending Physician (formerly pathologist) to the Methodist Episcopal Hospital, Philadelphia Cloth Price \$10.00 Pp 640, with 175 engravings and 10 colored plates Philadelphia Lea and Febiger, 1923

This volume presents in a detailed manner the author's extensive investigation of the diagnostic and therapeutic value of the nonsurgical drainage of the gall tract. Following an excellent chapter on the anatomy of the biliary system, the author devotes sections to a discussion of the fundamental principles on which the method is based, namely, the theoretical "law of contrary innervation" of S J Meltzer, and to a critical review of experimental work tending to cast doubt on the soundness of this underlying principle.

The technic of medical drainage of the gall tract is given in detail as well as the author's indications for its use in various pathologic and functional conditions. Numerous case protocols are appended to illustrate the employment of the procedure in the diagnosis and treatment of gall tract disease and other conditions in which its use depends on less well defined indications. Several of these protocols report cases of "biliousness" and "biliary migraine" treated by nonsurgical gall tract drainage. The reader, however, is left in some doubt as to the essential nature of "biliousness" and is not advised as to means of recognizing "biliary" migraine. Many will question the truth of the author's assumption that migraine is a disease of the liver, and will ask whether the clinical improvement noted in the migraine group in cases in which this method of treatment was used may not have been achieved largely by other therapeutic measures.

Dr W F Manges contributes an excellent chapter on roentgen-ray diagnosis of gallbladder disease.

Dr Lyon's volume may well be considered an authoritative exposition of the case for medical bile tract drainage and will prove of interest and value to the considerable number of physicians now using the method with a view of determining its ultimate value.

THE THERAPEUTIC USE OF DIGITALIS G CANBY ROBINSON, Professor of Medicine, Vanderbilt University Baltimore Price, \$2.50 Pp 144 Williams and Wilkins Co

This is the first of a series of "Medicine Monographs", the original appeared in *Medicine*.

The author states in the preface "In reviewing the extensive literature on the drugs of the digitalis group the writer has endeavored to keep constantly in mind the needs of the physician who is faced with the problems of the treatment of heart disease." In discussing the source of digitalis he calls attention to the value of American-grown digitalis which is equal in activity to that grown in Europe. In discussing biologic essays he favors the cat unit. The potency and permanency of digitalis preparations are reviewed in detail. A chapter devoted to the toxic effects of digitalis contains much valuable information. The therapeutic effects of digitalis is discussed under four heads: effect on the heart muscle, cardio-inhibitory mechanism, blood vessels and kidneys.

A chapter of twenty-seven pages is devoted to the use of digitalis in heart failure. This is subdivided into disturbed cardiomechanism, heart failure with normal cardiac mechanism, vulvular heart disease and disturbance of the

nervous mechanism There follows a chapter on digitalis in infectious diseases The question of dosage—intravenous, subcutaneous, intramuscular and by rectum—is discussed in a concise manner Reference 163 includes all the more important discussions on digitalis

There is a distinct need for a book of this character in which the entire subject is presented in a concise manner by a physician who is familiar with both pharmacology and clinical medicine It can be read or referred to with profit by every practitioner of medicine

TUBERCLE BACILLUS INFECTION AND TUBERCULOSIS IN MAN
AND ANIMALS ALBERT CALMETTE Authorized English translation by
WILLIAM B SOPR and GEORGE H SMITH 689 pages, 25 plates, 31 figures
Baltimore Williams & Wilkins Company, 1923

This is an excellent text on the subject mentioned in the title It contains detailed reference to the morphology, cultural characters, susceptibility to various agents, the chemical composition, toxins, tissue lesions, and mechanism of host infection of the tubercle bacillus Tuberculosis of the various tissues and organs is discussed fully Part two contains details regarding tuberculosis in animals other than man These chapters discuss the bovine and avian types and also the acid-fast bacilli of cold blooded animals Part three considers the tissue defense and the diagnosis of tuberculous infection Part four deals with the natural immunity and immunization against tuberculosis One chapter of this part considers briefly chemotherapy The text is especially valuable to those interested in more than clinical tuberculosis For the latter group, however, there is contained much useful information

INVESTIGATIONS INTO THE OCCURRENCE AND CLASSIFICATION
OF THE HAEMOGLOBINOPHILIC BACTERIA MARTIN KRISTENSEN
Copenhagen Levin & Monksgaard, 1922

This report of 272 pages and three plates concerns a review of the causal relationship of *B influensae* with the recent and the 1889-1892 pandemics of influenza To this are added cultural and morphologic studies of *B influenzac* by the author, as well as summaries of these features by others It is reasonable to conclude, writes the author, that *B influenzae* is not the primary influenza microbe The morphologic and cultural characteristics of *B influenzae* are given in detail A comparison of *B influenzac* with other haemoglobinophilic bacteria is given The text, therefore, appeals particularly to those interested in bacteriology

INFECTION AND RESISTANCE HANS ZINSSER Third edition, revised
666 pages New York The MacMillan Company, 1923

Zinsser's "Infection and Resistance" as a text needs no introduction to workers in immunity and the closely related medical sciences The third edition, thoroughly revised, contains complete accounts of immunity processes, with added interpretations which recent work in colloidal chemistry are making possible This text is invaluable to those interested in any phase of immunity, present or past

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AN ANALYSIS OF TWO HUNDRED AND TWENTY CASES OF ENDOCARDITIS

WITH SPECIAL REFERENCE TO THE SUBACUTE BACTERIAL TYPE¹

B J CLAWSON, M.D.
MINNEAPOLIS

The condition of the heart valves included in the term subacute bacterial endocarditis has within the last fifteen to twenty years created much interest. As early as 1885, Osler¹ described this condition in what he called malignant endocarditis. Horder² and Billings³ described it, in 1909, under the heading of infective endocarditis. Endocarditis lenta was the term used by Schottmuller⁴ in 1910, and in the same year the term subacute bacterial endocarditis was first used by Libman and Celler⁵. Munzer⁶ and Ruggeri⁷ used the term slow endocarditis. Various phases of the subject have been considered in France by Achard and Rouillard,⁸ Debré,⁹ and others, in Germany by Schottmuller,⁴ Munzer,⁶ Hassencamp¹⁰ and Moravitz,¹¹ in England by Lewis,¹² Horder,¹³ Poynton,¹⁴ Boyd,¹⁵ Cotton,¹⁶ Combs,¹⁷ Gibson,¹⁸ Gow¹⁹ and Starling,²⁰ in Canada by Murray and Lougheed,²¹ and in the United States by Libman and Celler,⁵ Baehr²² and others.

* From the Department of Pathology, University of Minnesota

1 Osler, W Brit M J **1** 467, 1885

2 Horder, T J Quart J Med **2** 289, 1909

3 Billings, Frank Chronic Infectious Endocarditis, Arch Int Med **4** 409 (Nov) 1909

4 Schottmuller Munchen med Wchnschr **57** 617, 1910

5 Libman, E, and Celler, H L Am J M Sc **140** 516, 1910

6 Munzer, E Zentralbl f inn Med **41** 282, 1920

7 Ruggeri Riforma med **36** 522, 1920

8 Achard, C, and Rouillard, J Bull et mem Soc med d hôp de Paris **44** 910, 1920

9 Debre R Rev de med **36** 199, 1919

10 Hassencamp, E Deutsch med Wchnschr **48** 1638, 1922

11 Moravitz, P Munchen med Wchnschr **68** 1478, 1921

12 Lewis, T Brit M J **2** 301, 1920

13 Horder, T Brit M J **2** 301, 1920

14 Poynton, F J Brit M J **2** 306, 1920

15 Boyd, F D Edinburgh M J **27** 129, 1921

16 Cotton, T F Brit M J **2** 851, 1920

17 Combs, C F Brit M J **2** 306, 1920, Quart J Med **15** 114, 1922

18 Gibson, A G Brit M J **2** 308, 1920

19 Gow, A E Brit M J **2** 307, 1920

20 Starling, H J Brit M J **2** 308, 1920

21 Murray, L M, and Lougheed, G W Canadian M A J **11** 666, 1921

22 Baehr, G, and Lande, H Glomerulonephritis as a Complication of Subacute Streptococcus Endocarditis, J A M A **75** 789 (Sept 18) 1920

An exact agreement among workers as to what is meant by subacute bacterial endocarditis has not been reached Libman²³ has included such conditions as are frequently called chronic ulcerative endocarditis, chronic malignant endocarditis and endocarditis lenta Valvular defects resulting from rheumatic and syphilitic infections and defects caused by congenital deformities and arteriosclerosis he would not consider as endocarditis He would classify endocarditis as rheumatic, syphilitic and bacterial The bacterial type he would divide into acute (lasting up to about six weeks) and subacute (lasting from four to eighteen months or more) Horder²⁴ would eliminate from the class subacute bacterial endocarditis such conditions as acute bacterial endocarditis, bacterial endocarditis associated with other diseases, acute or chronic and ulcerative endocarditis

A general uniformity of opinion exists among writers on the subject of subacute bacterial endocarditis in regard to a group of clinical and pathologic findings Clinically, the condition is characterized by an insidious onset, disability and loss of tone, sallow complexion, intermittent fever which is often not high and at times in the course of the disease may be absent for considerable periods, progressive anemia of the secondary type, joint pains and some articular swelling not so severe as in rheumatic fever, dyspnea, the presence of petechiae on the skin and conjunctivae, especially when they occur in recurrent crops, Osler's nodules, mild leukocytosis and the marked frequency of the finding of *Streptococcus viridans* in the blood The disease seems to prevail among persons from 20 to 45 years of age and frequently in persons who have had a previous attack of rheumatism This form is common among soldiers, as is pointed out by Becher²⁵ in Germany and Murray²¹ in Canada According to Hassencamp,¹⁰ it is on the increase in Germany, especially among ex-soldiers Lewis¹² thinks that it is much more common than has been generally believed and that it often escapes recognition Moravitz¹¹ says that it is generally not diagnosed properly but is frequently called incipient tuberculosis, anemia, malaria, etc In emphasizing the increased incidence since the war, Gow¹⁹ shows that in an English hospital there were seventeen cases of subacute bacterial endocarditis in 460 necropsies during a period of seventeen months, while in the same length of time since the war there were thirty cases in 345 necropsies Horder²⁴ found it occurring in England in the proportion of about 1 to 200 among patients admitted to the hospital in which he made his observations This form of endocarditis seldom has

23 Libman, E Am J M Sc **144** 313, 1912

24 Horder, T J Brit M J **2** 301, 1920

25 Becher, E Munchen med Wchnschr **68** 267, 1921

a duration of more than two to three years It is generally fatal, although recoveries have been reported by Libman²⁶ and Murray²⁷

The characteristic pathologic findings at necropsy are embolic processes (such as petechiae in the skin and conjunctivae, infarction of the spleen and kidneys, cerebral embolism and embolic glomerulonephritis), enlarged spleen, large and villous vegetations on leaflets otherwise normal or thickened from previous inflammation and involvement of the mural endocardium Pericarditis and myocarditis are seldom found Aschoff nodules in the myocardium are rare *Streptococcus viridans* is commonly found in the heart blood and on the injured valves

The purpose of this paper is to analyze 220 hearts which show the results of definite rheumatic or bacterial infections to determine whether a definite anatomic picture of subacute bacterial endocarditis exists and if so how it differs pathologically from other forms, such as primary and secondary acute bacterial and rheumatic endocarditis, and to study the origin and manner of development of old healed defective valves

Two hundred and twenty hearts with infectious valvular injuries were found in a series of 3,890 necropsies performed at the University of Minnesota during the years 1912 to 1922 One hundred and thirty-six hearts had been preserved and were available for examination The necropsy descriptions were used for the remaining eighty-four From one to three slides of heart, kidneys and liver from each necropsy were examined Only positive microscopic findings are conclusive, for it would be necessary to have sections from many different parts of organs in order to draw negative conclusions

These 220 hearts were separated by necropsy findings into two main groups hearts with active lesions and hearts with old healed defective valves The cases with active lesions were further divided into (1) bacterial endocarditis (those without an immediate association with rheumatism), and (2) rheumatic endocarditis (those immediately associated with acute rheumatic fever) The bacterial type was divided on the basis of the duration of the process into (a) subacute bacterial endocarditis with a clinical course of more than six weeks (usually from four to eighteen months or more), and (b) acute bacterial endocarditis with a duration of not more than six weeks The latter class was considered as primary acute bacterial endocarditis when no primary focus of infection existed and as secondary acute bacterial endocarditis when associated with another disease, acute or chronic

26 Libman, E Brit M J 2 304, 1920

27 Murray, L M Ann Clin Med 1 18, 1922

The classification adopted as a working basis in analyzing these hearts was, therefore

I Hearts with active lesions

- 1 Bacterial endocarditis
 - (a) subacute
 - (b) acute (primary, secondary)
- 2 Rheumatic endocarditis

II Hearts with old healed defective valves

Fifteen cases of bacterial endocarditis were classified as doubtful because the duration of the disease was unknown. It is seen in Table 1 that, of the 220 hearts, the subacute bacterial group comprises seventy-two (33 per cent), those with old healed valves sixty-four (29 per cent), the secondary acute bacterial forty-three (20 per cent), the primary acute bacterial seventeen (8 per cent), and the acute rheumatic nine (4 per cent).

TABLE 1—Relative Number of Each Kind of Valvular Disease Found in 220 Necropsies

Kind	Number	Percentage
Subacute bacterial endocarditis	72	32.7
Healed thickened valves	64	29.0
Secondary acute bacterial endocarditis	43	19.5
Acute bacterial endocarditis, independent	17	7.7
Acute rheumatic endocarditis	9	4.0
Doubtful	15	6.8

Three thousand eight hundred and ninety necropsies were performed from 1912 to 1922. The total number of hearts with valvular disease was 220, or 5.6 per cent.

ILLUSTRATIVE CASES OF EACH GROUP

Subacute Bacterial Endocarditis—A white boy, aged 18, admitted to the hospital on Aug 5, 1920, complained of weakness and fever. At the age of 6 he had had rheumatic attacks with pain in the joints, and at 10 he had had measles and mumps. He had had frequent attacks of sore throat. In the winter of 1919-1920 he had had influenza and pneumonia. About March, 1920, he noticed pain in the region of the spleen followed by chills and fever coming on about 4 o'clock each afternoon. Three weeks later he had attacks of precordial pain relieved by sitting up. Physical examination showed the heart to be enlarged and the spleen and liver palpable. The urine contained many leukocytes and red blood cells. The hemoglobin content was 31 per cent, the erythrocytes numbered 2,660,000. A blood culture made before death yielded a pure growth of *Streptococcus viridans*. The temperature was septic in type, running up to from 102 to 103 F each afternoon. During his stay in the hospital he developed at one time a left-sided hemiplegia. There was pain in the left arm and loss of radial pulse. He grew progressively worse until death on Oct 4, 1920. When examined at necropsy no edema was present. There was no excess fluid in the peritoneal, pleural or pericardial cavities. The pericardium was adherent to the heart over the entire anterior surface, with fibrous adhesions. The heart weighed 540 gm. The mitral valve leaflets were almost entirely covered with numerous vegetations which extended up on the wall of the auricle. The spleen was enlarged, weighing 310 gm and adherent to the

omentum A number of hard white infarcts measuring up to 4 cm in diameter were found The liver was enlarged, weighing 2,200 gm, and on section passive congestion was evident Over the surface of both kidneys puckered scars of healed infarcts were seen On the right side of the brain, there was a depression which on section showed a softened area 1 cm in diameter

Healed Defective Valves—A young white man, aged 27, admitted to the hospital on April 15, 1922, complained of hemoptysis, anasarca, precordial pains, dyspnea, weakness and palpitation He had chorea at the age of 4, with recurrences until the age of 6, and measles without complications at the age of 9 His first attack of rheumatism occurred at the age of 19 It lasted a month and involved all the joints They were red, swollen and painful At the age of 22 he had had a second attack lasting three months He had had frequent attacks of tonsillitis Following his second attack of rheumatism in 1917 he had developed slight dyspnea and palpitation on exertion This had cleared up in a short time In August, 1921, while working, he had developed a troublesome cough and expectorated bright red blood In January, 1922, he had had edema of the extremities for the first time Because of extreme dyspnea and weakness he entered the hospital He had to be propped up in bed to breathe The skin was slightly icteric, and the mucous membranes were cyanotic Death occurred on Oct 1, 1922, from heart failure At necropsy marked edema was present in the lower extremities, scrotum, penis, back, forearms and hands The skin was yellow The peritoneal cavity contained about 6 liters of straw colored fluid The right pleural cavity contained 200 cc of yellowish fluid, and the left 500 cc About 900 cc of clear fluid were found in the pericardial cavity The heart weighed 550 gm The edges of the tricuspid valves were replaced by firm fibrous scar tissue The orifice was greatly narrowed The mitral orifice was also greatly narrowed and the leaflets fused, thickened and calcified The aortic leaflets were distorted, but the orifice was not greatly narrowed The lungs were edematous The liver showed marked evidence of chronic passive congestion The spleen and kidneys were free from infarcts

Secondary Acute Bacterial Endocarditis—A white woman, aged 36, was admitted to the hospital on May 25, 1921 On April 14, she had been delivered of a full term baby, but had not had an attending physician The baby had died on April 24 from erysipelas and meningitis On the twentieth day after delivery, the patient developed swelling in the legs and a temperature of 103 F She died on May 31, 1921, from sepsis At necropsy the left leg and thigh were found to be markedly edematous, and the foot and leg half way up to the knee were gangrenous Some fibrinous adhesions were present in the pelvic cavity but no free pus On the aortic cusps were numerous pink vegetations, some of which were large The spleen was enlarged and contained two fresh infarcts No infarcts were found in the kidneys The uterus was soft and friable A thin serous fluid was present on the uterine mucosa The left common iliac vein was completely filled with a soft purulent thrombus The uterine plexus showed thrombosis Blood cultures made before death contained *Streptococcus hemolyticus*

Primary Acute Bacterial Endocarditis—A white woman, aged 34, who had always been well, was taken sick September 21 1919, with a chilly sensation, nausea and pain in the back She had no sore throat at the time The temperature, which was 104 F, continued until death on Sept 27, 1919 At necropsy no edema or jaundice was present No lesions were noted in the pelvis or about the appendix The heart weighed 370 gm Several large vegetations were present on the mitral valve The leaflets were thickened and the adjacent edges fused On the leaflets of the aortic valve there were two or three rather large vegetations The lungs showed a slight increase in amount of fluid The spleen was large, weighing 520 gm Several infarcts were found in the spleen and kidneys From cultures of the heart blood and spleen *Streptococcus hemolyticus* was grown

Acute Rheumatic Endocarditis—A young white girl, aged 9, admitted to the hospital on Nov 11, 1922, complained of dyspnea on exertion, nervousness and pain over the precordium. The present illness began in June, 1922, when she had an attack of acute rheumatism. There was multiple involvement. The joints were swollen, red and tender. The rheumatic attack lasted two weeks. The tonsils were enlarged and reddened. The temperature ranged from 99 to 101.5 F. The blood showed 70 per cent of hemoglobin, 3,950,000 red blood cells and 13,000 white cells. On Dec 2, 1922, she had a sudden collapse with marked dyspnea and cyanosis and died. At necropsy slight edema was noticed about the ankles and face. About 200 cc of clear fluid was present in the peritoneal cavity. The pleural cavities contained no excess fluid. The pericardial fluid was clear, but there were multiple fine nodules over the epicardial surface. Multiple small verrucous bodies with smooth surfaces were present on the under surface and on the edges of the mitral valves. Similar small globular structures were found on the under surface and on the edges of the cusps of the aortic valve and a few on the tricuspid. The lungs were grayish pink and feathery throughout. There was no evidence of infarcts in the spleen and kidneys. Blood cultures taken during life and at necropsy were negative.

TABLE 2—*Age and Sex Incidence*

Decade	Subacute Bacterial Endocarditis			Healed Thickened Valves			Secondary Acute Bacterial Endocarditis			Acute Bacterial Endocarditis, Independent			Acute Rheumatic Endocarditis			
	Fe	Male	Female	Fe	Male	Female	Fe	Male	Female	Fe	Male	Female	Fe	Male	Female	
1	0	1	1	1	0	1	1	0	1	0	0	0	0	2	2	
2	5	5	10	1	0	1	2	0	2	1	2	3	0	3	3	
3	13	4	17	7	4	11	1	8	9	2	1	3	2	1	3	
4	12	5	17	11	3	14	4	7	11	1	1	2	0	0	0	
5	14	1	15	13	3	16	5	2	7	1	2	3	1	0	1	
6	7	2	9	11	2	18	4	3	7	3	0	3	0	0	0	
7	2	0	2	4	1	5	4	1	5	2	1	3	0	0	0	
8	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	
9				2	0	2	1	0	1	0	0	0	0	0	0	
Totals	—	54	18	72	51	13	64	22	21	43	10	7	17	3	6	9

The ratio of males and females coming to necropsy is 2 : 1

AGE INCIDENCE

In his cases, Horder²⁴ found subacute bacterial endocarditis occurring between the ages of 15 and 50. Half of them occurred between the ages of 20 and 40. In Debré's⁹ analysis, 66 per cent of the cases occurred in patients between the ages of 15 and 30. He also found a few cases in persons above 30 and a few in children. M'Cartney²⁸ reported a case in a child 3½ weeks old, and cited the case of an infant 6 months old. In our cases, it is seen in Table 2 that the peak of incidence of the subacute bacterial and the secondary acute bacterial groups is in the third and fourth decades, of the old healed valve group in the fourth and fifth decades and of the acute bacterial and acute rheumatic groups in the second and third decades. Comparing the age incidence in cases of old valvular defects with cases of hyper-

tension hearts (with which they are apt to be confused clinically), it is found that the maximum age incidence in cases of hypertension hearts is in the sixth and seventh decades²⁹

SEX INCIDENCE

Males predominate in the subacute bacterial and old healed cases, while in the primary and secondary acute bacterial and acute rheumatic cases there is a prevalence of females. There is a high percentage of females in the secondary acute bacterial group, especially in the third and fourth decades. This is largely accounted for by the association of endocarditis with abortion and puerperal sepsis. This occurred nine times in the forty-three cases of secondary acute bacterial endocarditis. Rheumatic endocarditis is mainly a disease of youth but may occur later in life.

TABLE 3.—*Embolic Processes*

	Subacute Bacterial Endocarditis		Healed Thickened Valves		Secondary Acute Bacterial Endocarditis		Acute Bacterial Endocarditis, Independent		Acute Rheumatic Endocarditis	
	No	%	No	%	No	%	No	%	No	%
Petechiae	21	29.0	3	4.7	2	4.6	3	18.0	1	11.0
Infarct, spleen	34	47.0	10	15.5	15	35.0	7	41.0	0	0.0
Infarct, kidney	30	42.0	7	11.0	10	23.0	7	41.0	0	0.0
Paralysis	12	17.0	1	1.5	1	2.3	2	11.8	0	0.0
Cases with embolic processes	48	67.0	14	22.0	16	37.0	10	59.0	1	11.0
Cases with all four forms	1	1.4	0	0.0	0	0.0	0	0.0	0	0.0
Cases with both spleen and kidney involvement	14	19.0	6	9.0	9	21.0	6	35.0	0	0.0
Cases of embolism on basis of spleen, kidney and brain	45	62.5	12	19.0	16	37.0	9	53.0	0	0.0
Total embolic processes	105	36.5	21	8.0	28	16.0	19	28.0	1	2.8
Embotic glomerulonephritis	35	55.0	2	4.0	1	2.5	2	12.0	0	0.0

EMBOLIC PROCESSES

The frequent occurrence of embolic processes in subacute bacterial endocarditis has been emphasized by practically all who have written on the subject. Starling²⁰ found them in 58 per cent of his cases. Such processes are manifested before death as petechiae on the skin and conjunctivae, and by symptoms of cerebral embolism. At necropsy they are seen as infarcts of the spleen, kidneys and brain. The relative frequency of such processes is shown in Table 3. Petechiae were found by the clinician or pathologist in thirty-two (14.5 per cent) of the 220 cases. Of these thirty-two cases exhibiting petechiae, twenty-one (29 per cent) belonged to the subacute bacterial class, three (5 per cent) to the class with healed defective valves, two (5 per cent) to the secondary acute bacterial, three (18 per cent) to the primary acute bacterial, and one (11 per cent) to the acute rheumatic. This shows the percentage highest in the subacute and acute bacterial classes.

29 Bell, E. T. Personal communication

Petechiae occurred only once in the acute rheumatic group. As pointed out by Gibson,¹⁸ too much diagnostic importance must not be placed on petechiae, even when they occur in recurrent crops, for they may appear in other pathologic conditions, such as septicemia.

The most frequent manifestation of arterial embolism found at necropsy is the presence of infarcts in the spleen. In Starling's²⁰ seventeen cases of subacute bacterial endocarditis coming to necropsy he found infarcts in the spleen in twelve. In the 220 spleens in our series, infarction was found in sixty-eight (31 per cent). Its occurrence is more than twice as frequent as were the petechiae. As with the petechiae, the infarction of the spleen is more frequent in the subacute bacterial than in the other classes, but is relatively high in the acute forms. Infarcts were present in thirty-four (47 per cent) of the subacute bacterial cases, in ten (15.5 per cent) of the cases with old healed valves, in fifteen (35 per cent) of the secondary acute bacterial, in seven (41 per cent) of the primary acute bacterial, and in none of the acute rheumatic cases.

Infarction of the kidneys was common and of the embolic processes was next in frequency to infarction of the spleen. In many of the cases both kidneys showed infarcts, but in these statistics the presence of infarcts in either or both kidneys is reported as one. Infarction of the kidneys occurred fifty-seven times in the 220 cases, or in 26 per cent of them, only a little less frequently than infarction of the spleen. It was present in thirty (42 per cent) of the subacute bacterial cases, in seven (11 per cent) of the cases of the old healed defective valves, in ten (23 per cent) of the secondary acute bacterial, and in seven (41 per cent) of the primary acute bacterial cases, but in none of the acute rheumatic cases was infarction of the kidneys noted. In discussing embolic processes in subacute bacterial endocarditis, Horder¹³ states that the infarcts in subacute bacterial endocarditis are nonsuppurative, a characteristic which distinguishes them from the infarcts in the acute bacterial forms. The kidneys in forty-five subacute bacterial cases were examined for abscesses. In none of these was there any indication of abscesses. In ten of the kidneys of the thirty-two acute bacterial forms, abscesses were present. Abscesses were not found in the kidneys in any of the cases of acute rheumatic hearts. The findings show the more frequent occurrence of suppuration associated with the acute bacterial forms. The greater virulence of the organisms producing the acute bacterial forms as a rule will account for this.

Paralysis resulting from brain emboli was a frequent finding, occurring eighteen times (20 per cent) in the hearts examined. It was found in the different classes as follows: in the subacute bacterial twelve (17 per cent), in cases with old healed valves one (1.5 per

cent), in secondary acute bacterial one (2 per cent), in primary acute bacterial two (12 per cent), and in the acute rheumatic it did not occur at all.

Forty-eight (67 per cent) of subacute bacterial, fourteen (22 per cent) of the cases with defective valves, sixteen (37 per cent) of the secondary acute bacterial, ten (59 per cent) of the primary acute bacterial, and only one (11 per cent) of the acute rheumatic showed embolic processes in one or more forms. Only the subacute bacterial class contained a case having all four manifestations of emboli at the same time. The cases having infarction in both the spleen and kidneys are as follows: subacute bacterial fourteen (19 per cent), cases with defective valves six (9 per cent), secondary acute bacterial nine (21 per cent), primary acute bacterial six (35 per cent). This condition did not occur in the acute rheumatic hearts. Leaving out the petechiae as a consideration, since they may be caused by a variety of conditions other than embolic processes, on the basis of infarction of the spleen and kidneys and cerebral embolism, it is seen that forty-five (62 per cent) of the subacute bacterial, twelve (19 per cent) of those with defective valves, sixteen (37 per cent) of the secondary acute bacterial, nine (53 per cent) of the primary acute bacterial, and none of the acute rheumatic showed the presence of arterial embolism. When the total number of possible embolic processes, not including embolic glomerulonephritis, is noted, the various classes show the following number: subacute bacterial 105 (36 per cent), cases with defective valves 21 (8 per cent), secondary acute bacterial twenty-eight (16 per cent), primary acute bacterial nineteen (28 per cent), and acute rheumatic one (3 per cent).

The presence of embolic processes in the cases of old healed defective valves is probably to be explained as a result of a previous bacterial endocarditis. Most of such infarcts are old. The following case is one of the 220 cases which illustrate this condition.

A white man, aged 37, admitted to the hospital on April 29, 1912, complained of weakness, shortness of breath, pain in the precordium and back. He stated that he had never had venereal diseases, scarlet fever, measles, diphtheria, tonsillitis or rheumatism. His trouble began about fourteen years before with a dull pain in the region of the heart, weakness and shortness of breath. He had no edema at that time. Symptoms remained about the same until he became much worse four years previous to his coming to the hospital. During an attack which lasted about five months, anasarca and ascites were present. At necropsy, edema was present in the feet. The peritoneal cavity contained about 200 cc of a yellow fluid. The right pleural cavity contained a large amount of yellowish fluid. The pericardial cavity was greatly distended with a straw colored fluid. The heart weighed 660 gm. Whitish patches were noted in the endocardium in the right auricle. The mitral leaflets were fused, thickened and calcified, giving the fish mouth appearance. Several large deep reddish nodules were present immediately under the pleura of the right lung. On section these were found to be red and triangular in shape. The spleen weighed 270 gm. The

cut surface showed a whitish area, triangular in shape, with the base toward the surface. This area was from 4 to 5 cm wide and sharply demarcated. The liver weighed 2,300 gm and showed passive congestion. On the surface of both kidneys were deep depressions which on section showed the cortices replaced by masses of connective tissue sharply marked off from the surrounding cortex. Here there is no history of rheumatism. Old healed infarcts were present in both spleen and kidneys. The case strongly suggests a previous attack of bacterial endocarditis as the cause of defective valves.

It can be said in general that embolic processes have the highest incidence in subacute bacterial endocarditis, high in acute bacterial endocarditis, relatively low in cases with healed defective valves, and absent in the acute rheumatic cases. Abscesses when present as a result of infected emboli are associated with the acute forms. Anatomically, the presence of embolic processes seems to differentiate the active forms, subacute and acute bacterial, from the rheumatic. In cases of old healed defective valves, the presence of embolic processes, when we consider their absence in acute rheumatic cases, seems to indicate that healing of cases of primary or secondary acute bacterial or subacute bacterial endocarditis plays a rôle in the development of defective valves. The higher incidence of embolic processes in subacute bacterial endocarditis than in the acute, primary or secondary, might be accounted for by the fact that the vegetations have been present over a longer period of time and that the possibility of parts of the vegetations breaking off and causing a cerebral embolism or infarction of the spleen and kidneys is proportionately greater. The duration of the process should be considered in interpreting variations in findings in the acute and subacute bacterial forms of endocarditis. The presence of abscesses resulting from infected emboli is probably dependent on the virulence of the infective agent.

Embotic glomerulonephritis, as described by Loehlein³⁰ is common in subacute bacterial endocarditis. It is a condition, as pointed out by Baehr and Lande,²² in which there is an infarction of parts of the glomerular tufts resulting from bacterial emboli dislodged from the infected heart valve. It occurs rarely or not at all in other classes. Baehr and Lande considered it characteristic of subacute bacterial endocarditis. They examined slides from several places in each kidney. In our cases, the determination was made from an examination of one or two blocks. Our findings can be considered conclusive only so far as they are positive. The relative frequency with which this condition occurs is interesting (Table 3). The percentage of case incidence is high in subacute bacterial endocarditis, thirty-five (55 per cent), low in patients with old defective valves, two (4 per cent), in primary acute endocarditis, two (12 per cent), and in secondary acute, one

(25 per cent) It is absent in the rheumatic cases It is seen that this condition may be present in the old healed cases and in the acute forms in a few instances In one of the two old healed cases infarction of the kidney was present In neither case were bacteria found In one of the two cases of primary acute bacterial endocarditis septic infarcts were present Evidently, in rare cases both abscesses and embolic glomerulonephritis may occur at the same time In the other primary case, no infarcts were present In the secondary acute case *Streptococcus hemolyticus* was cultured from the blood It should also be noticed that embolic glomerulonephritis does not occur in the same proportion in the subacute bacterial endocarditis as do the other embolic processes This is accounted for probably by the degree of virulence of the organism in the bacterial emboli producing the embolic glomerulonephritis Apparently only the less virulent strains produce embolic glomerulonephritis The virulence of the organism is another factor always to keep in mind in interpreting processes associated with bacterial endocarditis

SPLENIC ENLARGEMENT

Splenic enlargement is a usual finding in cases of subacute bacterial endocarditis This has been emphasized by both clinicians and pathologists writing on the subject Arnett,³¹ in a study of splenic enlargement in 286 necropsies, found enlargement of the spleen in chronic passive congestion resulting from cardiac failure about one-half as frequent as in endocarditis Stirling,²⁰ in discussing the pathology of subacute bacterial endocarditis, reported enlarged spleens in sixteen of seventeen necropsies Enlargement of the spleen can occur in any of the types of endocarditis, even to quite an extent in the acute rheumatic The largest spleen found in our 220 cases was one weighing 1,400 gm in a case of subacute bacterial endocarditis The patient developed lobai pneumonia and at death *Streptococcus hemolyticus* was found in the blood Considering the spleen weighing over 200 gm as enlarged, enlargement is found in forty-five (62 per cent) of the subacute bacterial cases, in twenty-seven (42 per cent) of the cases with defective valves, in twenty-one (49 per cent) of the secondary acute bacterial cases, in twelve (71 per cent) of the acute bacterial cases, and in three (33 per cent) of the acute rheumatic cases (Table 4) With spleens of this size, little difference is noticed in the frequency of its enlargement in the different classes When 500 gm or more are considered as enlarged, the enlargement is more frequent in the bacterial types In subacute bacterial cases, such enlargement was found ten times (14 per cent), in cases with old healed valves once (15 per cent),

31 Arnett, J H Am J Med Sc 163 590, 1922

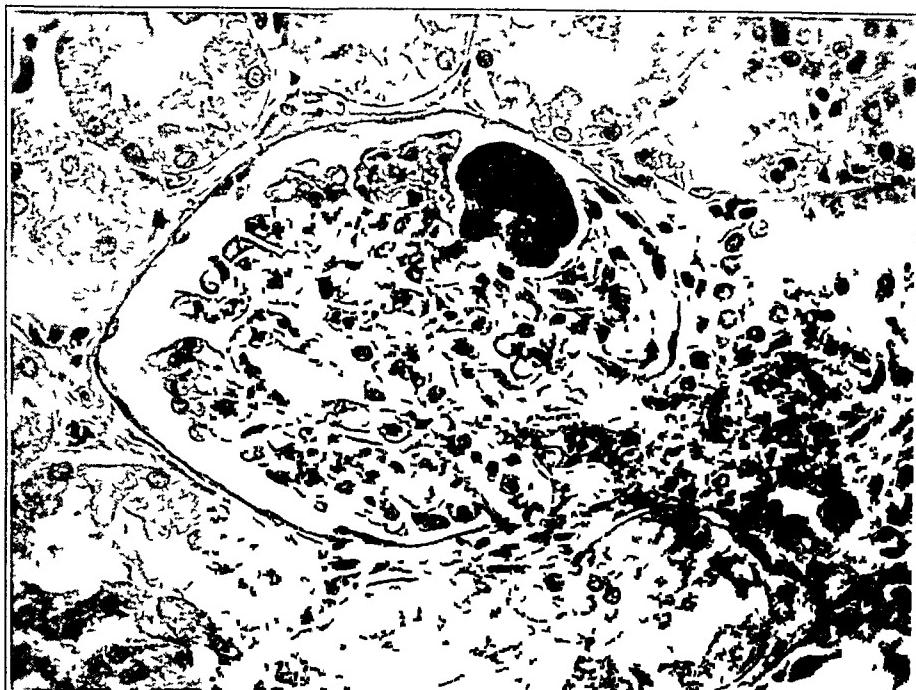


Fig 1.—A clump of streptococci lodged in a glomerular tuft

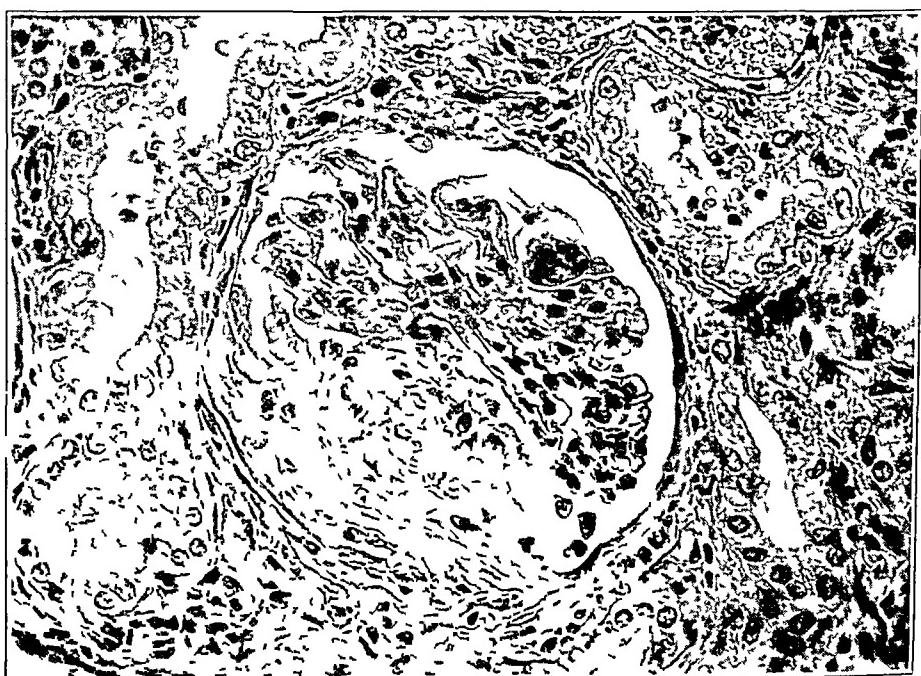


Fig 2.—Embolic glomerulonephritis in a case of subacute bacterial endocarditis

in the secondary acute bacterial five times (12 per cent), in the acute bacterial twice (11.7 per cent), and in the acute rheumatic not at all. Splenic enlargement is common in the subacute and acute bacterial forms and in the old healed valvular cases when enlargement not exceeding 500 gm is considered, but when spleens weighing over 500 gm are counted, the percentage in the bacterial forms is higher. It seems evident that splenic enlargement to the extent of being palpable would be much more common in bacterial endocarditis, acute or subacute, than in either the cases showing cardiac failure from defective valves or in the rheumatic cases. Marked enlargement of the spleen associated with cardiac disease results mainly from infection rather than from passive congestion. As in embolic processes splenic enlargement does not definitely separate subacute and acute bacterial cases of endocarditis, but it sets these off from the cases of acute rheumatic endocarditis.

TABLE 4.—*Enlarged Spleen*

Kind	200— 250	250— 300	300— 350	350— 400	400— 450	450— 500	Over 500	Per- centage Over 500	Total Per- centage
	200— 250	250— 300	300— 350	350— 400	400— 450	450— 500	Over 500		
Subacute bacterial en- docarditis	9	9	11	4	1	1	10	14.0	45
Healed thickened valves	11	3	6	3	2	1	1	1.5	27
Secondary acute bac- terial endocarditis	5	6	0	2	1	2	5	12.0	21
Acute bacterial endo- carditis independent	1	1	3	2	1	2	2	11.7	12
Acute rheumatic endo- carditis	2	0	1	0	0	0	0	0.0	3
									33.0

INVOLVEMENT OF THE ENDOCARDIUM

The vegetation itself, regardless of its location on the valve, has considerable significance, especially in differentiating the active bacterial forms from the rheumatic vegetations. Libman²⁶ describes the vegetations in the rheumatic hearts as being covered with endothelium, but Murray²⁷ found that the endothelium was not always present over the vegetations. Grossly, the vegetations in subacute bacterial endocarditis are usually large, pedunculated though sometimes sessile, villous and cauliflower-like. They are often soft, frequently calcified in parts, and often almost completely fill the orifices. Those in the primary and secondary bacterial cases, when examined grossly, are structurally similar to the subacute vegetations. Frequently they are smaller but not always. The acute forms, especially those of the secondary acute, are red, soft and velvety in appearance. While the vegetations of the subacute endocarditis cannot be differentiated grossly from the primary and secondary acute forms, all of these are decidedly different from those found in the rheumatic valves. In these the vegetations are

round or globular in shape, small (usually not more than from 2 to 5 mm in diameter), smooth and glistening (Fig 3) This explains why embolic processes are not present in such cases

Microscopically, the vegetations in the subacute and the acute forms of bacterial endocarditis seem to be similar They are essentially thrombi which are undergoing organization They are usually covered with bacteria, practically always streptococci (Fig 4) These, according to Libman,³² prevent the endothelium from growing over the organized thrombus The organization is conspicuous in being cellular and only slightly vascular There is no difference apparently between

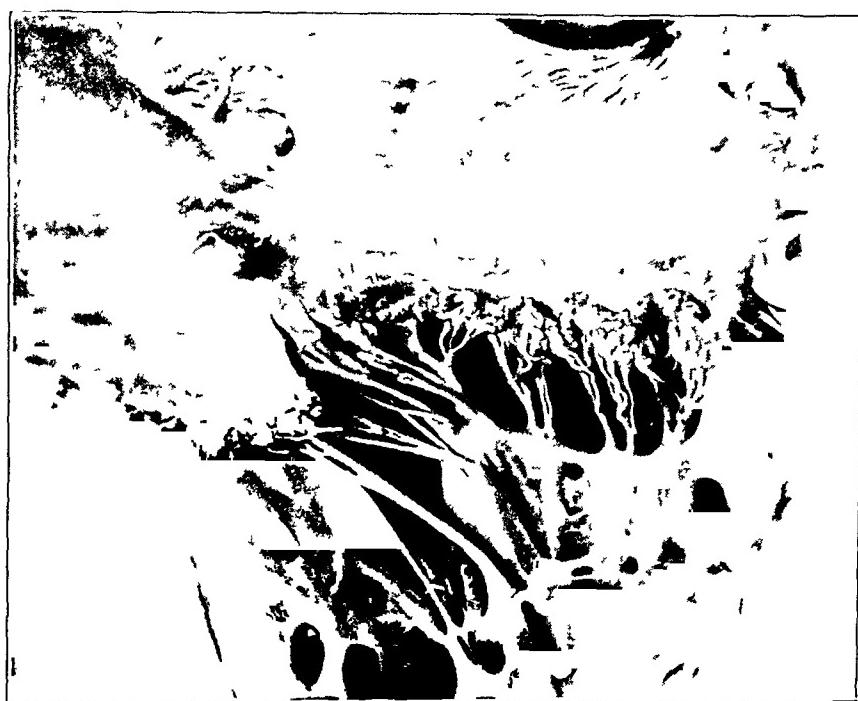


Fig 3—Vegetations in acute rheumatic endocarditis

the active bacterial forms Any of them may suppurate The microscopic picture of the rheumatic vegetation is different Baehr³³ describes the lesion as first being a proliferative inflammation over which the endothelial cells swell and desquamate The denuded areas are covered with agglutinated blood platelets The adjacent endothelium rapidly proliferates covering the surface of the blood platelet nodule and thus limiting the size Later the verruca becomes organized and a ridgelike scar is formed The lesion as shown in our section (Fig 5) is present within the nodular vegetation, which is covered with endo-

32 Libman, E Characterization of Various Forms of Endocarditis, J A M A 80 813 (March 24) 1923

33 Baehr, G, cited by Libman

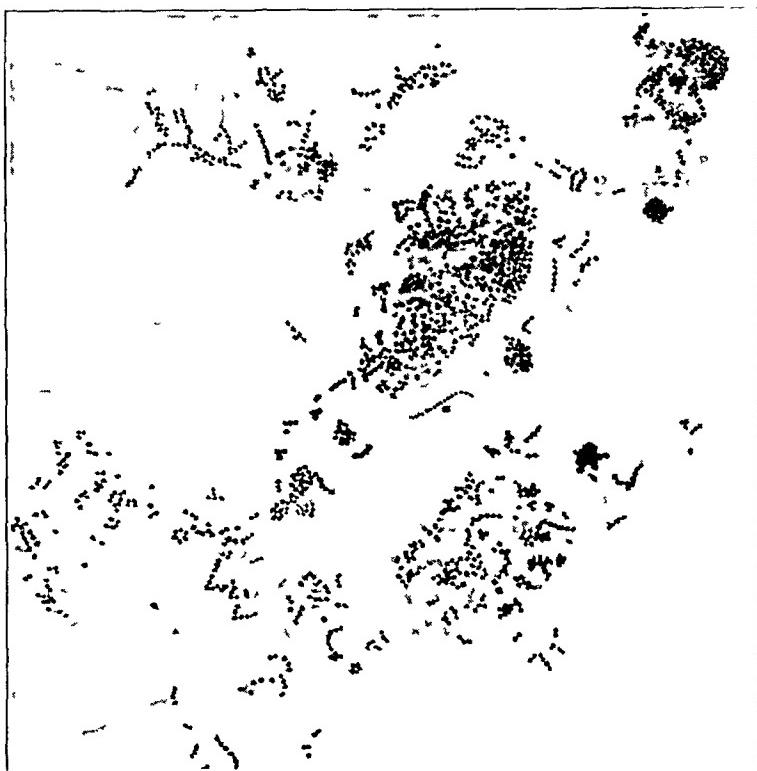


Fig 4.—Vegetation of subacute bacterial endocarditis showing streptococci

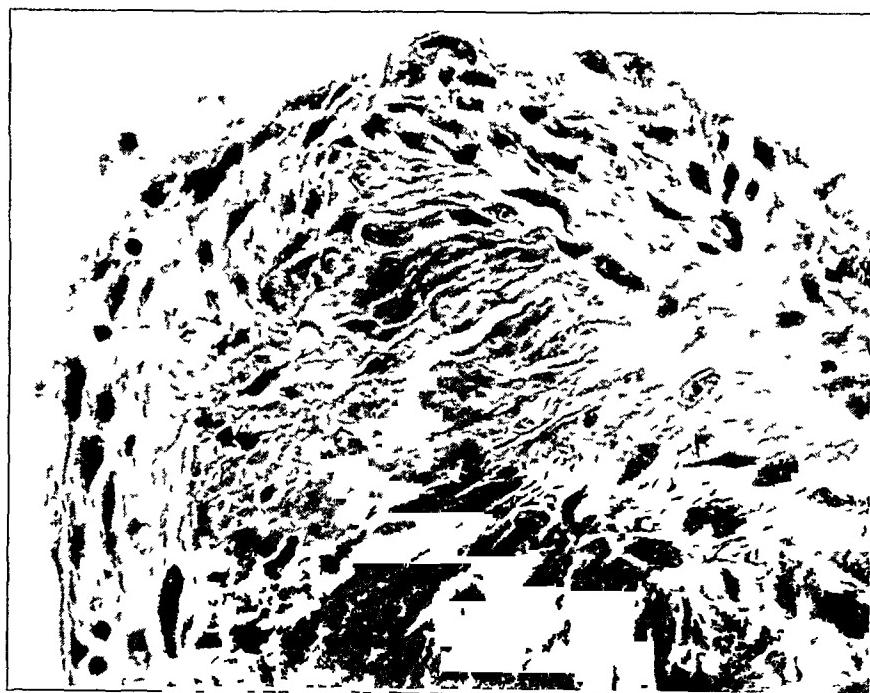


Fig 5.—Rheumatic vegetation showing hyalinized area within the nodule

thelium in many cases. There is little or no cellular exudate. The lesion is characterized by a hyalinized area (apparently hyalinized connective tissue) within the nodule, around which there is a marked proliferation. The reaction to the virus is characterized by proliferation rather than exudation. The endothelium may not cover the entire lesion, and the hyalinized material may extend beyond the endothelium, in this resembling the vegetation of the bacterial forms (Fig. 6). Whether the process is the same as the bacterial but slower, with rapid proliferation of connective tissue and endothelium, or whether it is strictly a proliferative process, is not entirely clear. Further work is

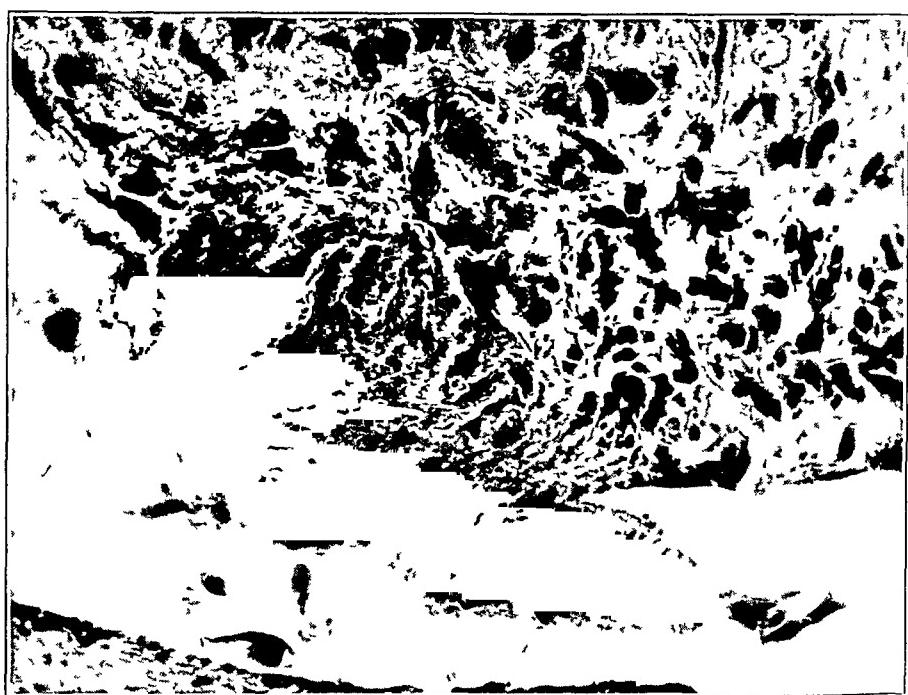


Fig 6.—Rheumatic vegetation showing the hyalinized material extending beyond the endothelium

being done to determine the process. In none of our rheumatic vegetations were bacteria found when stained, as were the bacterial vegetations, by the Gram-Weigert method. The vegetations of the subacute and primary and secondary acute bacterial endocarditis cannot be differentiated absolutely by either gross or microscopic examination, but they are easily differentiated from the type of vegetation found in the few hearts at our disposal, which were immediately associated with clinical cases of acute rheumatic fever. This decided difference between the bacterial and rheumatic types can apparently only be explained on the basis of the character of the lesion. A difference in virus is certainly strongly suggested.

The same heart may show lesions of rheumatic morphology on one valve and of bacterial morphology on another valve. This is especially seen in the following case.

A young white man, aged 23, admitted to the hospital on Nov 8, 1920, complained of pain in the joints (hips, knees, ankles, shoulders, elbows and back) and shortness of breath. During his stay in the hospital he had a slight rise in temperature and a slight leukocytosis. Roentgen-ray examination showed the heart to be enlarged. On Dec 1, 1920, he was discharged and on June 4, 1921, he was readmitted with a complaint of severe pain from hemorrhoids, dyspnea and some swelling of the ankles. At this time he again had a slight temperature and leukocytosis. He died on the date of admission, of cardiac failure. At necropsy edema was present in both legs. There was slight jaundice. About 200 cc of clear fluid were found in the peritoneal cavity. The heart was enlarged, weighing 575 gm. On the edges of the leaflets of the tricuspid valve were numerous small smooth round to globoid vegetations (rheumatic). The mitral valve was thickened, sclerotic and calcified, with a greatly narrowed orifice. On the surface of the thickened leaflets were numerous thick vegetations, some calcified and others pink and soft (bacterial). Both the spleen and kidneys were free from infarcts. The liver showed marked evidences of passive congestion.

TABLE 5.—*Involvement of Endocardium*

	Subacute Bacterial Endocarditis		Healed Thickened Valves		Secondary Acute Endocarditis		Acute Bacterial Endocarditis, Independent		Acute Rheumatic Endocarditis	
	No	%	No	%	No	%	No	%	No	%
Mitral	55	76	56	87.5	33	77	11	64	7	78
Aortic	34	47	40	62.5	11	33	8	41	6	67
Tricuspid	7	9.7	9	14	1	2.3	1	6	5	56
Mitral and aortic	19	26	27	42	3	7	1	6	0	0
Mitral, aortic and tricuspid	2	2.8	5	8	0	0	2	12	4	44
Auricle	11	15	0	0	0	0	0	0	0	0
Ventricle	16	22	0	0	3	7	0	0	0	0
Ulceration	19	26	0	0	2	5	3	17	0	0

The involvement of the auricular and ventricular endocardium associated with valvulitis has been reported as occurring only in subacute bacterial endocarditis. Hoide²⁴ refers to this condition and thinks that failure of typical signs of valvular injury may be accounted for by the occurrence of the infection on the mural endocardium only. In our 220 hearts, the valves affected in order of frequency were the mitral, aortic and tricuspid (Table 5). In the subacute bacterial cases, the auricular endocardium was involved in eleven (15 per cent) and the endocardium of the ventricle in sixteen (22 per cent). The secondary acute bacterial cases showed no auricular involvement, but in three (7 per cent) the ventricular endocardium was affected. Involvement of the mural endocardium is not found in the other classes. Anatomically the involvement of the mural endocardium is fairly characteristic of the subacute bacterial class, but may be present in the acute form. It is the strongest anatomic differentiation between subacute and acute bacterial forms. Perhaps the degree of difference could be

explained on the basis of the duration of the process so far as the acute and subacute bacterial forms are concerned, for in the longer duration of subacute bacterial endocarditis a greater possibility for spreading exists. This explanation does not hold with the rheumatic, for it may have a duration equal to that of subacute bacterial endocarditis.

The term ulcerative endocarditis has had a general use. To many the presence of embolic processes signifies the presence of ulcerated valves. If the breaking off of particles of vegetations is looked on as ulceration, it is common in the subacute and acute bacterial types, but if a destruction of valvular tissue or organized vegetations with sloughing is considered as ulceration, then it certainly is much less common. The latter condition is seen in Table 5 to be relatively rare, as it occurred in the subacute bacterial form nineteen times (26 per cent), in the cases with old healed valves not at all, in the secondary acute bacterial cases twice (5 per cent), in the primary acute bacterial cases three times (17 per cent), and not at all in the acute rheumatic cases. Ulceration was present twenty-seven times (17 per cent) in the 156 active cases of endocarditis, while embolic processes were present seventy-five times (48 per cent). It is obvious that to produce embolic processes it is not necessary to have ulcerated valves. The term ulcerative endocarditis when used to indicate the presence of embolic processes is not good, for in most cases no ulceration actually occurs. Ulcerated valves cannot be used as a basis to differentiate subacute and acute bacterial forms. Its presence would rule out rheumatic endocarditis.

IMPLANTATION ON PREVIOUSLY INJURED VALVES

Most observers agree that hearts with valvular defects are more susceptible to reinfection than hearts with normal valves and that in a high percentage of cases of subacute bacterial endocarditis there is a history of a previous valvulitis which has apparently healed. Combs,¹⁷ in a histologic examination of valves in subacute bacterial endocarditis, found that in most of the valves there had been a previous infection. In our seventy-two hearts grouping as subacute bacterial endocarditis, forty-one (57 per cent) anatomically showed valves which were thickened to such an extent that a previous involvement was evident. Decided evidence of previous thickening was shown in eleven (25.5 per cent) of the forty-three secondary acute bacterial cases, in twelve (71 per cent) of the seventeen primary acute bacterial cases, and in two (22 per cent) of the nine cases of the acute rheumatic hearts (Table 6). It seems apparent that the previously injured valve is less resistant to infection than the normal valve and that these valves are subject to infection in the acute bacterial and the rheumatic types as well as in the subacute bacterial. The condition is not specific of the subacute bacterial class.

PERICARDITIS

That rheumatic endocarditis is commonly associated with pericarditis and that in subacute bacterial endocarditis pericarditis is seldom found, was pointed out by Libman²⁶. In our 220 hearts a study of the frequency in each class is made (Table 6). Pericarditis from the gross determination was found to occur as acute or healed with about the same frequency (18 to 19 per cent) in all classes except in that of acute rheumatic hearts in which the percentage is very much higher (78 per cent). Microscopic evidence of pericarditis showed it to be even more common. Pericarditis is not only more frequent in the rheumatic class, but the rheumatic virus seems also to be the most frequent causal agent in producing pericarditis in hearts with bacterial types of endocarditis or in hearts with defective valves. Rheumatism preceded or was present in nine (69 per cent) of the thirteen cases of

TABLE 6.—Relation of Rheumatism to Active Lesions, Old Healed Lesions, Pericarditis and Previously Thickened Valves

	Sub acute Bacterial Endo- carditis		Healed Thick- ened Valves		Secon- dary Acute Bacterial Endo- carditis		Acute Bacterial Endo- carditis, Inde- pendent		Acute Rheu- matic Endo- carditis		Doubt- ful		Total	
	No	%	No	%	No	%	No	%	No	%	No	%		
History of rheumatism	36	50	19	29	6	14	5	29	9	100	5	33	80	
Pericarditis	13	18	12	19	8	18	6	3	18	7	78	4	27	47
Previously thickened valve	41	57			11	25	5	12	71	2	22	7	47	73
Rheumatism with thick- ened valve	27	37.5*			5	11.5*	4	23.5*	1	11*	2	13*	39	
		66**				45**		33**		33**		29**		
Rheumatism with per- carditis	9	12.5*	5	8*	2	4*	2	12*	7	78*	1	7*	26	
	69†		42†		25†		67†		100†		25†			

* Total percentage.

** Percentage of thickened valves preceded by rheumatism.

† Percentage of cases of pericarditis preceded by rheumatism, negative thirteen times.

pericarditis in the subacute bacterial class, in five (42 per cent) of the twelve hearts with old defective valves, in two (25 per cent) of the eight secondary acute bacterial, in two (67 per cent) of the three acute bacterial, and in seven (100 per cent) of the seven rheumatic hearts, or in twenty-six (55 per cent) of the total forty-seven cases of pericarditis. This seems to show that pericarditis is relatively infrequent in any but rheumatic hearts, except when rheumatism has preceded the attack of acute or subacute bacterial endocarditis and that in such conditions the rheumatic virus is generally responsible.

MYOCARDITIS

It has been stated that the myocardium is seldom involved in subacute bacterial endocarditis. Occasionally there is an interstitial exudate composed of large or small mononuclear cells. The acute forms are

reported as having polymorphonuclear cellular exudate which differentiates them from the subacute bacterial and rheumatic classes. In our series, the myocardium of fifty-four hearts with subacute bacterial endocarditis was examined (Table 7). Definite indications of inflammation were found in thirteen (24 per cent). The character of the exudate was mononuclear in all but two, in which polymorphonuclear leukocytes were found. In one of these, streptococci were found in the blood and on the heart valve in large numbers. In the other, there was no bacterial record. Forty-nine hearts showing primary acute or secondary acute bacterial endocarditis were examined microscopically. Twelve (24.5 per cent) of these showed exudative inflammation. Five were mononuclear and seven were polymorphonuclear in character. The myocardium has been reported to be involved in rheumatic endocarditis in a much higher percentage than in any of the other types. The type of inflammation is considered specific. Aschoff nodules containing mononuclear cells and multinuclear large cells are looked on as specific of rheumatic endocarditis. The myocardium of nine cases grouping clinically as rheumatic endocarditis was examined. In none of these was there a polymorphonuclear exudate. In nine (100 per cent) inflammation was indicated by mononuclear exudate, and in eight of the nine Aschoff nodules were present.

ASCHOFF NODULES

These nodules are reported to be found in the myocardium of rheumatic hearts and not in hearts of bacterial endocarditis. An examination of 156 hearts which showed healed valves or in which there was active endocarditis was made (Table 7). Fifty-four of these were of the subacute class, and in six the Aschoff nodules were found. A girl, aged 11, gave no history of rheumatism but had a history of cardiac trouble which was preceded about two years by chorea. A second patient had two previous attacks of rheumatism, the first eleven years and the second six years before death. A third patient had an attack of rheumatism ten years before. A fourth patient gave a history of painful and swollen joints several months prior to the recent attack, and a fifth patient gave a history of painful joints about five months before death. In all of these cases, there was a history of rheumatism except in one, but in this one there was a thickened valve which suggests a previous rheumatic infection. The longest interval between the rheumatic attack and the final illness, ten years, occurred in the third case. Eleven other patients with subacute bacterial endocarditis with a previous history of rheumatism of ten years or less had no Aschoff nodules in their myocardium. In these there was no absolute evidence that the Aschoff nodules did not exist. They might have been found by examining slides from other parts of the heart.

Thirty-nine hearts with old healed valves were examined, and in three of these the Aschoff nodules were observed. In the first two cases there was no history of a previous attack of rheumatism. No embolic processes were found in these at necropsy. This might suggest that these thickened valves were produced by the rheumatic virus. In the third case, a history of rheumatism five years before was recorded. Here the Aschoff nodules seemed to have remained for a period of five years. Three other cases with defective valves and a previous history of rheumatism of five years or less did not show Aschoff nodules.

The hearts of seventeen primary acute and thirty-two secondary acute cases of bacterial endocarditis were observed, and in these forty-nine Aschoff nodules were found three times (Table 7). In the first, a history of rheumatism a short time before was mentioned. In the second, there was no history of rheumatism, but there was a previously thickened valve and no evidence of embolic processes. Two other acute

TABLE 7.—*Relation of Myocarditis to Endocarditis*

Kind	Number Examined	Myocarditis		Mono nuclear Exudate	Poly-morpho-nuclear Exudate	Aschoff Nodules		Percentage
		Number	Per-cent-age			Number	Per-cent-age	
Subacute bacterial endocarditis	54	13	24	11	2	6	11	77
Healed thickened valves	39	6	15	6	0	3	7	
Secondary acute bacterial endocarditis and acute bacterial endocarditis, independent	49	12	24.5	5	7	3	6	
Acute rheumatic endocarditis	9	9	100	9	0	8	89	

cases with a history of rheumatism of four years or less previous to death were examined, but no Aschoff nodules were found.

In eight of the nine rheumatic hearts Aschoff nodules were found. It is seen that in this type the percentage is much higher than in the other classes. The findings in this series seem to show that the myocardium is involved in a much higher percentage in the rheumatic hearts than in either the acute or subacute bacterial classes. The polymorphonuclear type of cellular exudate is most common in the acute bacterial forms, rare in the subacute bacterial, and not found at all in purely rheumatic carditis. The Aschoff nodules are characteristic of rheumatic carditis, and when they are found in other types there has been a previous rheumatic infection. These bodies may remain as long as ten years after infection, but on the other hand they apparently may disappear in much less time.

RHEUMATISM

The frequency of an attack of acute rheumatism previous to attacks of subacute bacterial endocarditis has been emphasized by many writers. It has been thought the chief cause of previously thickened valves on

which fresh vegetations commonly develop Libman²⁶ emphasized the fact that rheumatic endocarditis may be acute, recurrent or chronic It is a common finding to have one attack of rheumatism follow another Just how a rheumatic valve progresses to extreme thickening and deformity is not entirely clear, but in some cases at least it seems to be through recurrent or continuous infections with the rheumatic virus The following case in our series seems to show this continuous process The patient died when the process was still in progress

A white girl, aged 14, was first admitted to the hospital on April 9, 1912, with cardiac trouble She had acute rheumatic arthritis when 9 years of age She remained in the hospital until May 1, 1912 She improved and was discharged with a diagnosis of mitral stenosis In June, 1913, she had a severe attack of tonsillitis The cardiac condition immediately became worse, and she suffered from rheumatic pains in the fingers She was readmitted to the hospital on July 15, 1913 The tonsils were enlarged and inflamed There were subcutaneous rheumatic nodules on the fingers During the first week in August she developed chorea, which ran a severe course On Sept 16, 1913, after a tonsillectomy, she became irrational On Sept 22, 1913, she became unconscious The next day her temperature rose from 98 to 104 F She died on Sept 26, 1913

At necropsy no edema was noted The pericardial cavity was completely obliterated by fibrous adhesions The heart was greatly enlarged The leaflets of the tricuspid valve were thickened On the ventral surface near the margins of the leaflets were numerous small globoid vegetations The mitral orifice was distinctly narrowed The leaflets of the mitral valve were thickened and showed numerous similar globoid nodules No indications of infarction were found in the spleen or kidneys The liver showed passive hyperemia In this case there were thickened valves on top of which were active rheumatic vegetations From the history it would seem that the thickened valves were caused by the rheumatic virus

In our cases, a history in which rheumatism was mentioned occurred ninety-three times (Table 6) Eighty (36 per cent) of these gave a positive history of rheumatic fever and thirteen a negative history The number of positive cases of rheumatism is probably greater than the recorded cases show In comparing the different classes, it is seen that, aside from the acute rheumatic class itself, the subacute bacterial class shows the highest case incidence of a previous attack of rheumatism In seventy-two cases of subacute bacterial endocarditis a previous attack of rheumatism occurred in thirty-six (50 per cent) A previous history of rheumatism was present in nineteen (29 per cent) of the cases of old healed valves, in six (14 per cent) of the cases of secondary acute bacterial endocarditis and in five (29 per cent) of the acute bacterial class

Previously thickened valves are probably produced by the rheumatic virus in more cases than by any other infective agent Of the forty-one previously thickened valves in the subacute bacterial cases, twenty-seven (66 per cent) were preceded by an attack of rheumatism A previous attack of rheumatism was present in the other classes with previously

thickened valves as follows Five (45 per cent) of the eleven secondary acute bacterial, four (33 per cent) of the twelve acute bacterial, and one (33 per cent) of the three rheumatic hearts

These findings show that a previous rheumatic infection is frequent in cases of endocarditis, especially in the subacute bacterial types. They also indicate that rheumatism plays an important rôle in producing thickening of the valve leaflets in both the old healed valve group and in the cases of subacute bacterial endocarditis with previously thickened valves

BACTERIOLOGY

Horder²⁴ says he thinks that bacteria are present in the blood and on the valves throughout the course of the disease in subacute bacterial endocarditis, but Libman²⁶ is of the opinion that there may be a bacteria-free stage. In Gow's¹⁹ opinion the finding of the organism in the blood stream is of great diagnostic importance, but conversely he considers the failure to find the organism of little importance. Boyd¹⁵ found that streptococci may be adhering to the cusps when the blood stream is free. All have found that *Streptococcus viridans* is the chief organism in the subacute bacterial endocarditis and that the acute bacterial endocarditis is produced generally by *Streptococcus hemolyticus*, staphylococcus and pneumococcus. It is believed by most workers that rheumatic endocarditis results from an unknown virus, but Poynett¹⁴ says he feels certain, on the other hand, that this type too is produced by *Streptococcus viridans*. Combs¹⁷ suspects that rheumatic endocarditis may be produced by *Streptococcus viridans* and the anatomic difference may be a result of different degrees of resistance on the part of the host. Murray²⁷ obtained a lower percentage of *Streptococcus viridans* (80 per cent) than Libman²⁶ in the subacute bacterial class, and in one series he and Lougheed²¹ recorded finding sixty-six per cent of *Streptococcus hemolyticus* in cases of endocarditis resembling subacute bacterial endocarditis. Curschman³⁴ reported twelve cases of subacute bacterial endocarditis in five of which *Streptococcus hemolyticus* was found. Combs¹⁷ believes the infecting organism is comparatively unimportant and is not constant. Horder²⁴ stresses the fact that the organism producing subacute bacterial endocarditis is one of low virulence. This we find important in considering why certain strains produce a definite type of endocarditis. Both Libman³² and Kinsella³⁵ found that the blood of patients having subacute bacterial endocarditis had agglutinins and complement-fixing bodies for homologous strains of nonhemolytic streptococci isolated from the blood. They

³⁴ Curschman Munchen med Wchnschr **69** 419, 1922

³⁵ Kinsella, R A Streptococcus Endocarditis, Arch Int Med **19** 367 (March) 1917

found that this was not true in cases of rheumatic endocarditis in which streptococci were found in the blood Kinsella found no biologic or immunologic constancy between strains isolated from different cases of subacute bacterial endocarditis

In our 220 cases, there are only seventy-one in which there is a bacteriologic report (Table 8). In forty-six of these, positive bacteriologic findings are given. A negative report is given in twenty-five. Thirty of the seventy-one cases reported are classified as subacute bacterial endocarditis, and positive findings were obtained in twenty-two. *Streptococcus viridans* was found ten times, *Streptococcus hemolyticus* eight times, the staphylococcus twice, and the pneumococcus once. While this might suggest that *Streptococcus hemolyticus* frequently produces subacute bacterial endocarditis, it is necessary to take into consideration that in every case but one the organism was isolated from the heart blood at necropsy. It has been our experience

TABLE 8.—*Bacteriology*

Kind	Cases Reported	Positive Findings	Negative Findings	<i>Viridans</i>	<i>Hemolyticus</i>	<i>Staphylococcus</i>	<i>Pneumococcus</i>	<i>Streptococcus</i>
Subacute bacterial endocarditis	30	22	8	10	8	2	1	1
Healed thickened valves	13	4	9	1	2	1	0	0
Secondary acute bacterial endocarditis	17	14	3	2	6	3	3	0
Acute bacterial endocarditis, independent	6	4	2	0	3	1	0	0
Acute rheumatic endocarditis	5	2	3	1*	0	0	1	0
Total	71	46	25	14	19	7	5	1

* Pericardial fluid

that the frequency of *Streptococcus hemolyticus* as an agonal invader is much greater than that of *Streptococcus viridans*. The one case with antemortem findings gave a history of middle ear infection previous to the heart trouble. Four of the thirteen cases of hearts with old healed valves gave positive bacterial findings in a blood culture. One contained *Streptococcus viridans*, two *Streptococcus hemolyticus* and one *Staphylococcus aureus*. In the primary and secondary acute forms, *Streptococcus hemolyticus* was present more frequently. In the acute rheumatic forms, *Streptococcus viridans* was found once and the pneumococcus once. While our bacterial findings are not extensive enough to merit definite conclusions, it is suggested, as Murray and Cuischman reported, that *Streptococcus hemolyticus* may not be an uncommon etiologic factor in producing the subacute bacterial endocarditis and that it is the usual organism producing the acute types. It is likely that the virulence of the organism rather than the kind determines the course that the vegetative endocarditis will take.

CAUSE OF DEATH

There seems to be a rather general agreement with Horder²⁴ that in the major part of the course of subacute bacterial endocarditis, cardiac symptoms are not conspicuous. He found death occurring from toxemia, from heart failure, from uremia or from cerebral or coronary embolism. While cardiac symptoms may not be common early in the course of the disease, at death evidences of cardiac failure are conspicuous findings. In this series evidence of cardiac failure, as manifested by edema in its various forms and passive congestion of the liver, is common (Table 9). In fifty-nine (82 per cent) of the seventy-two cases of subacute bacterial endocarditis, edema was present (as edema seen externally) as hydrothorax, hypercardium or ascites. It was present in forty-seven (73 per cent) of the cases with old healed valves, in sixteen (37 per cent) of the secondary acute bacterial cases, in six (35 per cent) of the acute bacterial cases and in four (44 per cent) of

TABLE 9.—*Evidence of Cardiac Failure*

	Subacute Bacterial Endocarditis		Healed Thickened Valves		Secondary Acute Bacterial Endocarditis		Acute Bacterial Endocarditis, Independent		Acute Rheumatic Endocarditis	
	No	%	No	%	No	%	No	%	No	%
Edema	59	82	47	73	16	37	6	35	4	44
Passive hyperemia of the liver	65	90	58	91	25	58	13	76.5	9	100

the cases of acute rheumatic endocarditis. The lowest incidence is found in acute cases. Passive hyperemia of the liver was present in a higher percentage in all the classes than was edema. Infarction of the lungs was not an uncommon finding.

Various causes of death were evident in the subacute bacterial class as cardiac failure, sepsis, cerebral embolism, bronchopneumonia and lobar pneumonia, but by far the most frequent cause was cardiac failure. This condition was not infrequently complicated with other causes. In the cases with old healed valves the only cause of death worthy of note was cardiac failure. In the secondary acute bacterial cases the causes were more varied, as cardiac failure, sepsis, accident, miliary tuberculosis, carcinoma of different parts, bronchopneumonia and lobar pneumonia, starvation, chronic pulmonary tuberculosis, peritonitis, pericarditis, acute poliomyelitis, pernicious anemia, diabetes, myelogenous leukemia and Addison's disease. Chief among these causes is sepsis. In the acute bacterial class, as in the subacute bacterial, cardiac failure as a cause of death predominated. Cardiac failure and pericarditis rank as the chief causes of death in cases of acute rheumatic endo-

carditis It is obvious that, while various conditions produce death in endocarditis, cardiac failure is the common condition which directly or indirectly results in death

In the analysis of these 220 hearts, two main conditions are met the actively inflamed valves and the healed thickened valves with their associated pathology The active progressive cases may be placed in two groups which apparently are differentiated by practically all tests applied The first is the simple or verrucous endocarditis (rheumatic endocarditis), and the second, with the more villous lesion of the valves, might be included in the term bacterial endocarditis These two forms not only differ pathologically, but they also seem to be separated clinically The former is practically always associated with acute rheumatic fever or chorea and occurs as a primary infection rather early in life It is characterized by small, rounded and smooth vegetations which are apparently a result of proliferative inflammation Bacteria are not found in the vegetations In practically all cases there is an immediate association with pericarditis and myocarditis In the latter a special form of inflammatory reaction (Aschoff nodules) is practically always found Embolic processes, because of the firmness of the vegetations, do not occur The lesions are confined to the valvular endocardium The valves, once injured, become more susceptible to reinfection with the same virus or with bacteria, usually streptococci The spleen may be moderately enlarged This type is seldom fatal at the time of the active process In the few cases in which it does prove fatal the causes of death are usually cardiac failure and pericarditis It is the usual cause of the thickened healed valves which later in life commonly result in death from cardiac decompensation Not infrequently the healing of bacterial endocarditis leaves a deformed thickened valve

The second group cannot be divided into subgroups as easily pathologically as it can clinically Its vegetations are large, friable, generally filled with bacteria and tend to spread to the mural endocardium, depending on the duration of the process Myocarditis and pericarditis are rarely associated with this group Embolic processes are common Embolic glomerulonephritis occurs in cases with a slow process Previous attacks of rheumatism with rheumatic endocarditis greatly predispose to this form Death usually results from cardiac failure Since bacteria are generally found in the blood and on the valves, it seems advisable to use the etiologic basis for classification and call this form bacterial endocarditis The clinical terms acute and subacute bacterial endocarditis are valuable, for they include the duration and the etiology, the chief factors concerned in interpreting endocarditis The acute bacterial form may further be divided into primary and secondary acute endocarditis depending on whether it develops independently or as a result of some definite focus of infection Since ulcer-

tion of the valves is not common, the term ulcerative endocarditis is misleading. It would seem that the clinical terms subacute and acute bacterial endocarditis would be the most useful for the present, until the etiology of rheumatic endocarditis is definitely established. The terms endocarditis lenta and slow endocarditis have a clinical significance and a meaning similar to subacute bacterial endocarditis. Confusion may be avoided by using the term endocarditis for the active processes and defective valves for the healed processes.

CONCLUSIONS

Death occurring from cardiac failure before the age of 40 is practically always a result of valvular injury. The injury may be an acute process or a healed thickened condition resulting from a previous valvulitis.

Endocarditis associated immediately with acute rheumatism (rheumatic endocarditis) seldom causes immediate death. When in rare cases death does occur, it usually results from pericarditis and cardiac failure.

Emolic processes are common in all forms of bacterial endocarditis.

These processes are most frequent in the subacute bacterial form. This probably can be accounted for by the longer duration. Embolic processes do not seem to occur in acute rheumatic endocarditis.

Emolic glomerulonephritis is rarely found in any form of endocarditis except in subacute bacterial endocarditis in which it occurs in a high percentage of cases. Its occurrence seems to bear no direct relationship to other forms of embolic processes. The chief factor determining its presence seems to be the presence of organisms of low virulence on the heart valves. *Streptococcus viridans* is the usual organism, but the condition may be produced by *Streptococcus hemolyticus*.

The presence of embolic processes in cases with healed defective valves suggests that bacterial forms of endocarditis not infrequently heal, since in rheumatic endocarditis embolic processes are not found.

Splenic enlargement (to the extent of being palpable) associated with cardiac trouble generally indicates an active inflammatory condition of the valves rather than an enlargement from passive congestion.

The vegetations in acute and subacute bacterial endocarditis cannot be differentiated. They are essentially thrombi. The rheumatic vegetations are easily differentiated from the bacterial. They seem to be a condition resulting from a proliferative type of inflammation.

The active involvement of the auricular and ventricular endocardium rarely occurs except in subacute bacterial endocarditis. This is probably accounted for by the longer duration of the process in the subacute form.

Valvular ulceration is not a common finding. It occurs most frequently in the subacute bacterial class. Apparently it never occurs in rheumatic endocarditis. The term ulcerative endocarditis should not be used to indicate the presence of embolic processes, for the presence of embolic processes bears no direct relationship to ulcerated valves.

Previously injured valves are apparently more susceptible to infection than normal valves. In most cases they seem to have resulted from rheumatic infection, often recurrent and chronic, but they may be produced by the healing of bacterial infected valves.

Pericarditis is generally present in rheumatic endocarditis. It is seldom found in bacterial endocarditis not preceded by a rheumatic infection.

Myocarditis is practically always associated with rheumatic endocarditis but seldom occurs in the bacterial forms.

The presence of Aschoff nodules is apparently specific of a rheumatic infection. They may be found in the myocardium of cases with active bacterial valvulitis or in cases with healed defective valves when there has been a fairly recent previous attack of rheumatic carditis.

A rheumatic infection commonly precedes subacute bacterial endocarditis and is not infrequent in the other forms.

The finding of *Streptococcus viridans* in the blood in a case of endocarditis indicates a subacute bacterial form. The presence of *Streptococcus hemolyticus* or staphylococcus generally indicates an acute form of bacterial endocarditis, but by no means rules out the subacute form.

Whether a case of bacterial endocarditis will take an acute or subacute course depends on the virulence of the organism rather than on the kind.

The chief cause of death in endocarditis is cardiac decompensation.

Apparently the two main factors to keep in mind in interpreting variations in the findings in bacterial endocarditis are the duration of the process and the virulence of the organism producing the lesion. The former seems to be dependent on the latter.

THE EFFECT OF CERTAIN PAST DISEASES ON VITAL CAPACITY *

W P SHEPARD, B S, M D

MINNEAPOLIS

In seeking normal standards on which to base vital capacity readings, practically all investigators have found a considerable percentage of unexplained low readings in persons supposed to be normal. That there is a decided variation in the lung capacity of normal persons cannot be questioned, though recent work has tended to reduce this variation by corrections for age, sex, weight, height, surface area, chest circumference, sitting height, etc. In going over the vital capacity records recently of 1,304 male university students selected at random, we¹ pointed out that many of the low readings could be accounted for on the basis of past or present diseases. The present study was undertaken with a view to noting the effect of certain past intrathoracic diseases on the vital capacity. Few, if any, of the series reported heretofore have been correlated with as complete a history and physical examination as was available in the series here reported.

The Student's Health Service records of 1,517 male students comprising the freshman class entering the University of Minnesota in the fall of 1922 were available. The histories of these men were taken by medical students who filled out uniform blanks at the time of the entrance physical examinations. The examinations were conducted by the combined staffs of the health service and physical education department (fifteen physicians and twelve nurses), augmented by sufficient medical students and clerks to do the routine recording. Those students giving histories of epidemic influenza, pneumonia, pleurisy, pulmonary tuberculosis or heart disease, and those who at the subsequent examination showed physical signs of pleurisy, tuberculosis or organic heart disease, were selected for special study. Vital capacity readings were taken on all of the 1,517 students with a Sanborn water spirometer, a nurse and medical student especially instructed in the use of the machine being detailed to procure readings. Ample time was allowed each student to have the machine explained and to be given a minimum of three trials, the highest being recorded as his vital capacity. Standing height and

* From the Student's Health Service and Department of Preventive Medicine and Public Health, Medical School, University of Minnesota.

* Read before the combined Lymanhurst and Parkview Sanatorium staffs, June 26, 1923.

1 Shepard, W P, and Myers, J A Journal-Lancet 43 14, 355 (July 15) 1923

weight were measured with students stripped. Sitting height was taken according to the method of Dreyer,² with the students stripped. Chest circumference was measured at the level of the fourth rib on deep inspiration and deep expiration, and the computed mean was used as recommended by Parmenter and Gray.³ Surface area was computed from the height and weight according to the formulas of Du Bois and Du Bois.⁴ With these basic data, the vital capacity was reckoned in percentage of normal by the use of the tables of Myers,⁵ and a determination obtained according to (1) weight, (2) sitting height, (3) surface area and (4) chest circumference. These four determinations were then averaged and this figure taken as the person's vital capacity in percentage of normal.

Curves used in the figures for the usual distribution of vital capacities for male students were computed from the present series of

TABLE 1.—*Distribution of Vital Capacity in Diseases Studied*

Percentage Normal Vital Capacity	Epidemic Influenza		Pneumonia		Pleurisy		Tuberculosis		Cardiac	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Under 70	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
71 to 75	2	0.6	1	0.5	0	0.0	2	10.0	0	0.0
76 to 80	7	2.1	6	3.2	3	5.4	2	10.0	0	0.0
81 to 85	8	2.4	8	4.2	6	10.0	1	5.0	1	7.1
86 to 90	18	5.4	14	7.4	8	14.5	5	25.0	3	21.4
91 to 95	48	14.4	26	13.8	12	21.8	4	20.0	1	7.1
96 to 100	62	18.6	41	21.7	7	12.7	2	10.0	0	0.0
101 to 105	67	20.1	31	16.4	6	10.9	1	5.0	2	14.3
106 to 110	86	10.8	31	16.4	6	10.9	0	0.0	3	21.4
111 to 115	44	13.2	17	8.9	2	3.6	1	5.0	4	28.6
116 to 120	26	7.8	9	4.8	4	7.3	2	10.0	0	0.0
Over 120	15	4.5	5	2.6	1	1.9	0	0.0	0	0.0
Totals	333	99.9	189	99.9	55	99.9	20	100.0	14	99.9

1,517 and the previous series of 1,304, a total of 2,821. These vary slightly from the distribution reported by Hewlett and Jackson⁶ and Myers and Myers⁷ for male college students.

In each disease studied the distribution of vital capacities in both number of cases and percentage is shown in Table 1. The percentage of normal vital capacity in the first column is the average of the four determinations as described above. The number of cases under each

2 Dreyer, J., and Hanson, J. F. The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921.

3 Parmenter, D. C., and Gray, Horace. Chest Measurement as a Gage of Body Weight, J. A. M. A. 79:26, 2159 (Dec 23) 1922.

4 Du Bois, D., and Du Bois, E. F. A Formula to Estimate Approximate Surface Area if Height and Weight Be Known, Arch. Int. Med. 17:863 (June) 1916.

5 Myers, J. A. A Method for Quickly Obtaining the Percentage of an Individual's Theoretical Normal Vital Capacity of the Lungs, Am. Rev. Tuberculosis 7:161 (May) 1923.

6 Hewlett, A. W., and Jackson, N. R. The Vital Capacity in a Group of College Students, Arch. Int. Med. 29:515 (April) 1922.

7 Myers, J. A., and Myers, Frank J. Journal-Lancet 43:276 (June 1) 1923.

heading having vital capacities from 81 to 85 per cent of normal, 86 to 90 per cent, 91 to 95 per cent, etc., is listed opposite the appropriate heading. The incidence percentage of the various vital capacities is then shown in the column beside the number of cases.

A curve is prepared for each of the diseases studied on which the normal distribution of vital capacities computed from a total of 2,821 male students is shown in a heavy black line. Superimposed on this curve is the distribution of vital capacities in the particular disease group under consideration, shown by a light black line. The ordinate in each figure represents the incidence percentage of the various vital capacities, as shown in Table 1. The abscissa in each figure represents the vital capacities averaged and expressed in percentage of normal, as shown in the first column of Table 1. With this arrangement, it will be seen that any agent tending to diminish vital capacity will result in a lowering of the height of the distribution curve and in a shifting of the curve to the left. To illustrate the relative amounts of reduction in each of these diseases, the areas between curves are shaded whenever the disease curve is either lowered or shifted to the left. Roughly, then, the amount of reduction of vital capacity in a group of students giving histories of influenza, pneumonia, pleurisy, etc., may be estimated by the size of the area which is shaded.

INFLUENZA

In view of the frequency of pulmonary complications incident to the epidemic influenza of 1918 and 1919, and since many of these patients were unable to procure adequate medical attention and did not know whether or not pneumonia developed, this group was included for study. Only those who gave a history of influenza between 1917 and 1920 were considered. These numbered 333 cases out of the total of 1,517. The vital capacities of this group are listed in Table 1 and compared to the normal distribution in Chart 1. It will be seen that there is a slight lowering and shifting to the left of the influenza curve, indicating a slight reduction in vital capacity in the group as a whole. The significance of so slight a reduction may well be questioned as being within the limits of error of the method employed.

PNEUMONIA

There were 189 students who gave histories of pneumonia. Unfortunately, no differentiation could be made between lobar pneumonia and bronchopneumonia, and nothing was known of the severity of the disease. The age of the person at the time of the attack was given in each case. The vital capacities of this group are listed in Table 1 and illustrated in comparison to the normal in Chart 2. Here again, there

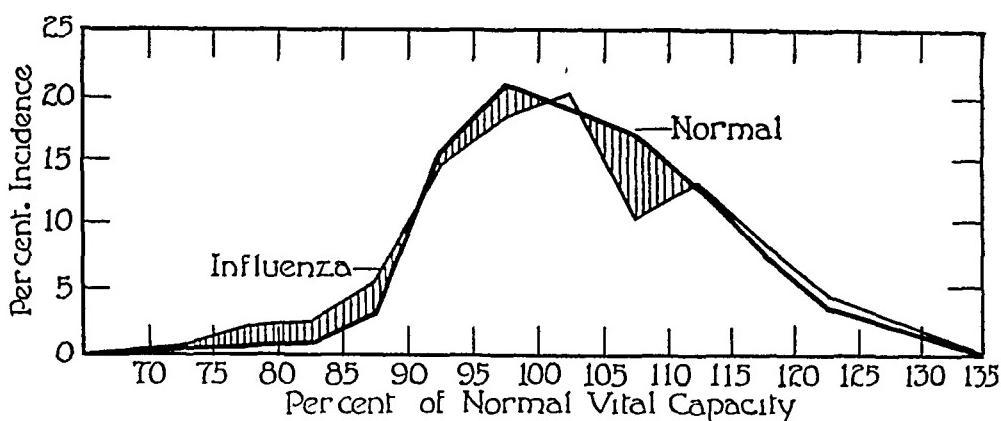


Chart 1—Remaining effect of epidemic influenza on vital capacity (333 cases).

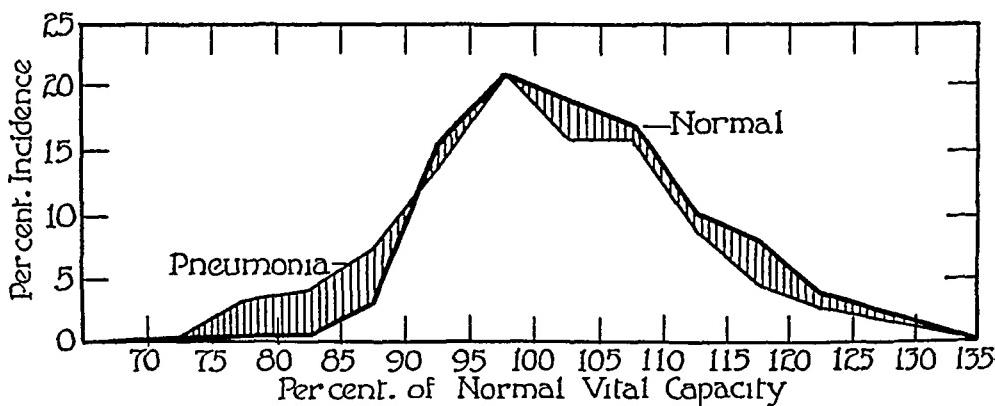


Chart 2—Remaining effect of pneumonia on vital capacity (189 cases).

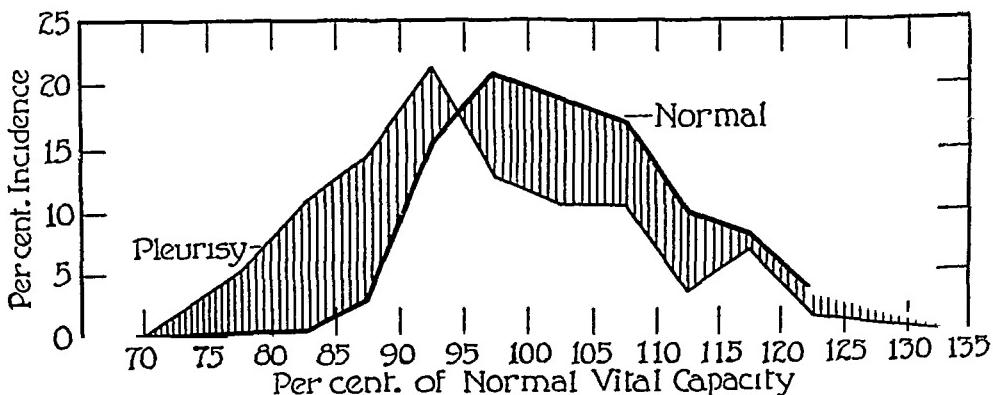


Chart 3—Remaining effect of pleurisy on vital capacity (fifty-five cases).

is a slight but definite lowering of the curve and a shifting to the left, a little more marked in this group than in the influenza series. The size of the shaded area is somewhat increased in this over that of the influenza figure. Here, again, the reduction is so slight as to be of questionable significance.

Recent studies by Stewart and Sheets,⁸ Wilson and Edwards⁹ and Emerson and Green¹⁰ have attracted attention to the vital capacities of children in health and disease. Apparently no special study was made of pneumonia. Several students in the present series were observed who had a low vital capacity without demonstrable cause even after repeated physical examinations over a period of several months. The only factor common to all these students was that they had had severe pneumonia at ages below 5 years. For this reason this entire group was analyzed from the standpoint of age at which pneumonia was contracted.

TABLE 2—Effect of Age When Person Had Pneumonia on Vital Capacity

	Total Cases	Cases Below 90% of Normal	Percentage Below Normal
Pneumonia under age 2	29	5	17.2
Pneumonia between ages of 2 to 5	44	2	4.5
Pneumonia between ages of 5 to 10	49	8	16.6
Pneumonia between ages of 10 to 20	67	10	15.0

Results are shown in Table 2 in which it is seen that there is apparently a slight increase in the number of low vital capacity readings when pneumonia was contracted at earlier ages, but the difference is slight.

PLEURISY

In considering pleurisy, only those who gave definite histories of severe attacks or repeated mild attacks or those who showed physical signs of pleurisy on physical examination were considered. These numbered fifty-five out of the total of 1,517. The vital capacities are listed in Table 1 and illustrated in comparison to the normal in Chart 3. This is the first figure that shows a definite reduction in vital capacity of the group as a whole. There is a marked lowering of the height of the curve and a shifting to the left. The shaded area is considerably increased over that in the preceding two charts.

⁸ Stewart, C A, and Sheets, O B. The Value of the Determination of Vital Capacity of the Lungs in the Diagnosis and Prognosis of Pulmonary Tuberculosis in Children, *Journal-Lancet* **42** 253 (May 15) 1922. Stewart, C A. The Vital Capacity of the Lungs of Children in Health and Disease, *Am J Dis Child* **24** 451 (Dec) 1922.

⁹ Wilson, May J, and Edwards, D J. Standards for Normal Vital Capacity for Children, the Lung Capacity in Certain Intrathoracic Conditions, *Am J Dis Child* **22** 443 (May) 1921.

¹⁰ Emerson, P W, and Green, H. Vital Capacity of the Lungs of Children, *Am J Dis Child* **22** 202 (March) 1921.

TUBERCULOSIS

Only cases in which there was a history of a diagnosis of tuberculosis together with prolonged sanatorium treatment or in which there were physical signs together with a history of a previous diagnosis were considered. Twenty such cases were found. The lung capacities are recorded in Table 1 and illustrated in Chart 4. So far as could be determined by entrance examination and subsequent observation, all cases were arrested. While the total number is small, the curve indicated a marked reduction in lung capacity of the group as a whole. These findings are in accord with those of Dreyer,¹¹ Myers,¹² Wilson and Edwards,⁹ Stewart and Sheets,⁸ all of whom find a reduction in vital capacity in tuberculosis.

HEART DISEASE

Only those persons who gave a history of heart disease with decompensation or who showed definite physical signs of organic disease together with some impairment of their physical condition were considered. The total was fourteen cases. Here again the series is small, but there is a definite lowering of vital capacity, as shown in Table 1 and Chart 5. All cases were apparently compensated at the time of examination and through six months' subsequent observation. This is contributory to the findings of Lattimore,¹³ Ulrich and Nathanson,¹⁴ who have studied vital capacity in various cardiac conditions.

CONCLUSIONS

1 Vital capacity is studied in 611 male university students who gave histories of influenza, pneumonia, pleurisy, pulmonary tuberculosis or heart disease. These are compared to vital capacity readings in 2,821 male students.

2 Each person's vital capacity is computed by averaging four determinations, namely weight, sitting height, surface area and chest circumference. The result is expressed as percentage of normal.

3 Influenza and pneumonia appear to lower the vital capacity of a large group, although the change is slight.

11 Dreyer, G., and Burrell, L. S. T. Vital Capacity Constants Applied to Pulmonary Tuberculosis, *Lancet* **2** 374 (Aug.) 1922.

12 Myers, J. A. A Comparison of Vital Capacity Readings and X-Ray Findings in Pulmonary Tuberculosis, Tr 17th Annual Meeting of National Tuberculosis Assn, 1922, p. 136.

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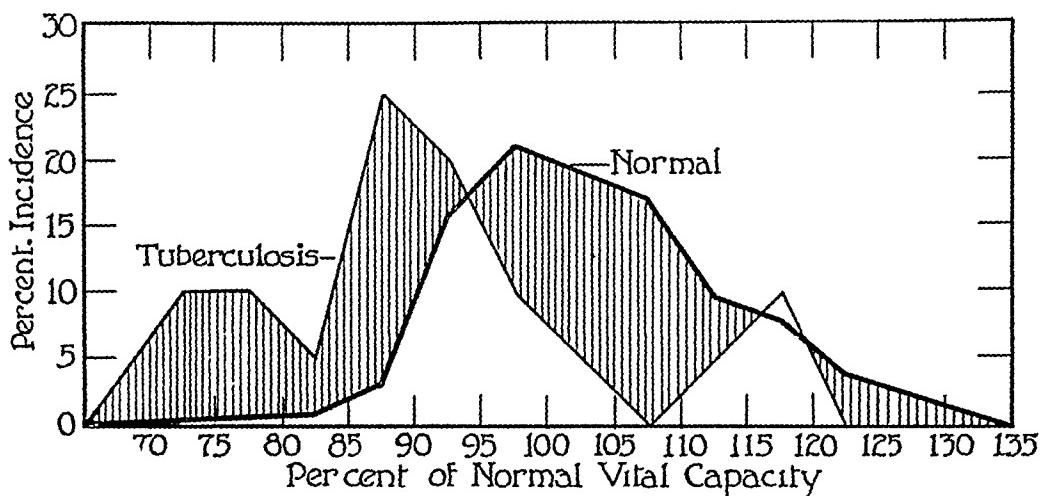


Chart 4.—Remaining effect of pulmonary tuberculosis on vital capacity (twenty cases)

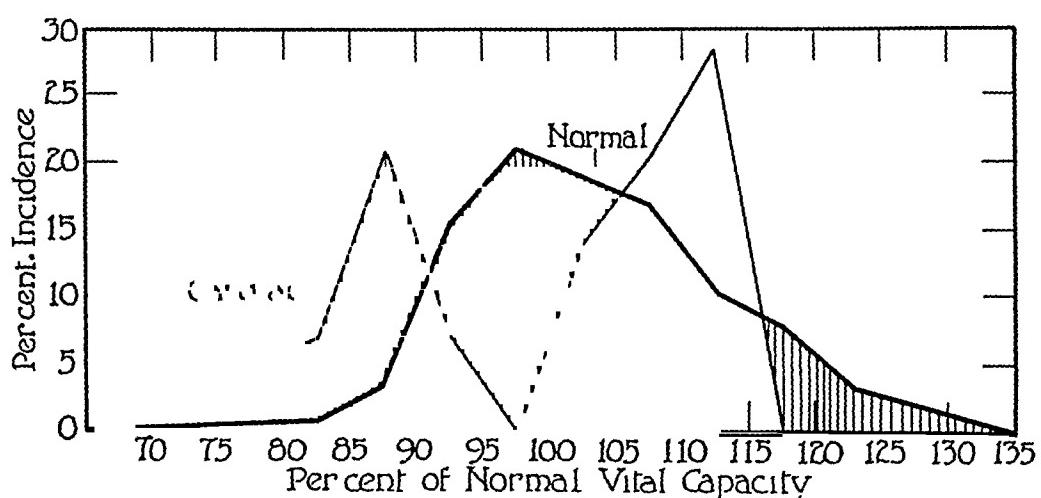


Chart 5.—Remaining effect of cardiac disease on vital capacity (fourteen cases)

4 Pneumonia varies but slightly in its effect on the vital capacity, according to the age contracted

5 When pleurisy, pulmonary tuberculosis or organic heart disease is included among the past diseases of a group of persons, there is apparently a definite and probably a permanent lowering of the vital capacity of that group as a whole

PROPERTIES OF YOUNG ERYTHROCYTES IN RELATION TO AGGLUTINATION AND THEIR BEHAVIOR IN HEMORRHAGE AND TRANSFUSION¹

RAPHAEL ISAACS, M.D.

BOSTON

In repeating the work of Ashby,¹ while studying the length of life of red blood corpuscles by the transfusion and agglutination method, it was found that in many patients more than 1 per cent of their red cells could not be agglutinated by serums, even before transfusion. The cells which did not agglutinate were found to consist of reticulocytes, normoblasts and cells with various types of "inclusion granules." The nature of these cells and their behavior under various conditions was studied in fifteen patients with various types of anemias in the wards of the Peter Bent Brigham Hospital, ten dogs and 130 normal persons.

The method of Ashby is based on the fact that the cells of Type II patients who have been transfused with Type IV (Moss) blood can be subsequently separated by agglutination with Type IV serum, which leaves the Type IV cells free. Under such conditions normal, non-transfused persons will have all of their cells agglutinated with the exception of about 20,000 to 50,000 per cubic millimeter, which remain free. Deducting this amount from the free cells of the transfused patient Ashby, and more recently Wearn, Warren and Ames,² studied the blood of patients with various types of diseases, and found that, after transfusion, the minimum of 1 per cent not agglutinated was not reached until from fifty-nine to 113 days, with an average of eighty-three days.

MATERIALS AND METHODS

The dog was found to be a suitable animal for experimental purposes. Ottenberg, Kaliski and Friedman³ showed that dogs possessed iso-agglutinins and isoagglutinins. Observations were also made on transfused and nontransfused human patients of different

¹This paper is No. 31 of a series of papers on the physiology and pathology of the blood from the Harvard Medical School and Allied Hospitals, a part of the expense of which has been defrayed by a grant from the Proctor Fund for the Study of Chronic Disease.

¹Ashby, Winifred. The Determination of the Length of Life of Transfused Corpuscles in Man, *J. Exper. Med.* **29** 267 (March) 1919.

²Wearn, Joseph T., Warren, Sylvia, and Ames, Olivia. The Length of Life of Transfused Erythrocytes in Patients with Primary and Secondary Anæmia, *Arch. Int. Med.* **29** 527 (April) 1922.

³Ottenberg, R., Kaliski, D. J., and Friedman, S. S. Experimental Agglutinative and Hemolytic Transfusions, *J. M. Res.* **23** 141 (May) 1913.

types, as well as on normal human beings. The blood of a group of ten dogs was matched, the corpuscles, serum and plasma of each being compared with serum, plasma and corpuscles of all the series. No effort was made to study type groups, although cases were found to correspond in their behavior to the four human groups, with an additional type in which two dogs would be mutually compatible (serum and corpuscles against corpuscles and serum) and thus apparently identical, but a third dog could be found whose serum agglutinated the corpuscles of one, but not the other. Dogs of this type, when transfused, were likely to have their type change suddenly after the transfusion, either to the type of the donor or to another type. Ottenberg, Kaliski and Friedman³ noted similar changes of type in dogs. An effort was made to use dogs whose breed was fairly similar, although pure, pedigreed strains were not used.

The method of counting unagglutinated cells was originally that of Ashby, later modified to overcome some technical difficulties. The blood was taken from a razor cut at the base of the ear, at the same time of the day and before the dogs had any food or drink. United States Bureau of Standards pipets and slides were used to calibrate the apparatus used. Serum was stored in ampules made of glass tubing having a diameter of about 5 mm., and kept in a cold room (4 degrees) when not in use. The same serum was used throughout most of the parallel experiments, and new serums were checked up by comparison with the old. It was found that serum kept best when it was placed in larger ampules made of hard glass test tubes. When tubes are freshly drawn out in a flame, the inside becomes coated with a soluble base which makes the serum alkaline. It is necessary to wash this out and dry the tube. If alcohol or ether is used for drying, it must be thoroughly removed as traces dissolved in the serum hasten hemolysis when corpuscles are added.

In making the serum, blood was drawn into centrifuge tubes and centrifugation at high speed was started before clotting took place. The corpuscles were separated, and on clotting a water-clear serum was obtained. Hemolysis takes place easily in dog's blood, and it was found necessary to separate the corpuscles quickly. Hemoglobin in the serum did not appear to influence the agglutination, but it was avoided in order to have the known factors as nearly similar as possible in different sets of serums.

Ashby's original method is, briefly, as follows. The blood of the recipient is drawn to the 0.5 mark in a leukocyte counting pipet, and is diluted to the 11 mark with 1 part of Group IV (Moss) serum in 20 parts of a 4.4 per cent solution of sodium citrate. After thorough mixing, the contents are expelled into a small test tube and incubated for forty minutes at 37°C., with thorough shaking every ten minutes.

The test tube is then placed in the icebox over night. In the morning the mixture is shaken, and a drop transferred to the hemocytometer slide, and the free cells counted.

We found it necessary to modify this method for dogs as hemolysis set in after from three and one-half to four hours under the conditions of our experiments. It was also noted, in the case of human blood, that after shaking the test tube and pouring out the blood, many of the single, free corpuscles remained adherent to the test tube, as shown by examination of the tube under the microscope. The agglutination in dogs is much weaker than in human blood, and the clumps of cells are more easily disturbed by shaking.

The following method was then devised. Blood from the patient or animal was drawn up to the 0.5 mark in a leukocyte counting pipet, and diluted to the 1.1 mark with a 0.85 per cent sodium chloride solution in distilled water, containing also 0.2 per cent sodium citrate. The first drop was blown out after thorough shaking, and the rest expelled into a small vial containing a glass bead. A red cell counting pipet having an accurately graduated stem was then selected, and the freshly shaken blood was drawn up to the 0.2 mark. Agglutinating serum was then drawn in until the solutions reached the 1 mark of the stem. This was then expelled on the table of a round moat type of hemocytometer slide, stirred with a glass rod (avoiding scratching of the ruled lines) and a grease-free cover applied. This was then kept in a moist chamber at from 18 to 22°C and counts of nonagglutinated cells were made from time to time as in making an ordinary blood count. A duplicate set was always made. The serum was so chosen that it agglutinated the recipient's cells (when the patient or animal was transfused) but had no agglutinating effect on the donor's corpuscles.

The dilution of 2 parts diluted blood (1:20) to 8 parts of serum was chosen after many tests of varying dilutions, because this gives just enough cells to about cover the hemocytometer table (with a count of 5 million) without crowding. In the older method there was always a question of cells mechanically covered by clumps. In some experiments the cover was raised at intervals and the contents stirred. It was found, however, that the cells had enough motility to enter the clump formation without stirring. In control slides with a nonagglutinating serum and with the saline-citrate solution and serum there was no tendency to clump even after hours. The dilution error could be kept within 1 to 2 per cent by this method.

Experiments were conducted to note the effect of varying hydrogen-ion concentrations. It was found that the buffering properties of the serum took care of all the probable variations of this technic. Serum made acid increased the rate of hemolysis, but agglutination was not more complete.

Temperature was found to vary the rate of hemolysis, so that if too warm, hemolysis set in before agglutination was complete. At the lower temperatures hemolysis was delayed, and the maximum agglutination was reached. Hemolysis and agglutination proceeded independently of each other. In dog's blood at temperatures above 22°C it was found that hemolysis began before agglutination was complete under the conditions of these experiments.

Under these conditions, with the calcium bound by citrate in the diluted corpuscles, and with the traces of the animal's own plasma in the corpuscle suspension, the maximum agglutination with dog's blood was reached in from two and one-half to three and one-half hours at from 18 to 20°C and in human beings in from twenty to twenty-four hours, a slight change taking place during the succeeding twenty-four hours.

The quantitative data concerning the rate of agglutination under the varying conditions are published separately.

Contact hemolysis (with glass) was avoided in this method by the protective action of the original and added serum, as demonstrated by Fenn.⁴ Rouleau formation was a source of trouble with some serums. If a dog was transfused with a second dog's blood, and the serum of the second used to agglutinate the corpuscles of the first in subsequent examinations (as using a Type IV [Moss] serum to agglutinate Type II corpuscles in the man) the donors' corpuscles, meeting their own serum, formed rouleaux. Such cases could not be used for these data. However, the continued formation of rouleaux under these conditions gave a clue as to the survival of the donor's corpuscles, and they were not recognized after the third or fourth day by this method. Rouleau formation and agglutination may be seen simultaneously in preparations of blood from transfused patients or animals.

Experiments using serum from the same dog instead of saline solution for dilution showed little difference in the end-result, with the disadvantage of rouleau formation, which frequently took place in the serum. In dogs whose "type" changed after a transfusion, the serum or plasma, saved from blood taken before the transfusion, agglutinated the cells and thus could not be used for diluting purposes. This agglutination was not so complete as with a foreign serum.

To avoid the addition of any saline solutions or of sodium citrate, experiments were carried out using blood defibrinated with glass beads. This was soon found to be unsuitable, as there is a "selective" factor in which some of the cells (young forms) were not included in the

⁴ Fenn, Wallace O. Hemolysis of Erythrocytes in Contact with Glass, J Exper Med 35:271 (Feb.) 1922.

strands of clot, whereas many mature forms were thus removed, producing a difference in the composition of the remaining cells.

Washed corpuscles were unsatisfactory in the dog, as hemolysis sets in quickly in dog's blood, and the relative composition (number of different types of red cells) was then changed.

Blood for transfusion in dogs was taken from the jugular vein and made to 0.2 per cent sodium citrate, usually with the crystals, or in a few experiments with a 10 per cent aqueous solution. Citration was used on the dog's blood, as this was the method used with the patients. Washed corpuscles were used in one experiment and the results compared with the whole blood. The blood was transfused through the jugular vein in the dogs, no anesthetic being used, as the dogs were very quiet and did not seem to be disturbed by the procedures. In making the daily counts, the dogs soon learned to jump on to the table and assume the proper position of their own accord.

It was soon found that after maximum agglutination of many patients' and some dogs' blood had been reached, there were often a great number of free, nonagglutinated cells, exceeding the 1 per cent set as the normal by Ashby for human blood. All variations in technic were tried, and the percentage still remained high in nontransfused persons. The problem of the cells which would not agglutinate was then studied.

It was first noted that in bloods containing many reticulated red cells, the nonagglutinable cell number was greater than in bloods containing fewer of these cells. Quantitative studies were then started, comparing the number of cells which would not agglutinate with the number of reticulated cells. The latter were counted in smears vitally stained with cresyl blue and counterstained with Wright's stain using the details given by Cunningham⁵. Usually 1,000 cells were counted, occasionally more (10,000). A close correspondence was noted in the two figures, in spite of the many sources of error in these methods. With the reticulated cells, stippled cells, cells showing other basophilic phenomena and cells showing large intracellular, refractive granules were studied.

Intracellular granules of four types were differentiated in the red cells of human and dog's blood, in blood showing evidences of regeneration.

1. Brilliant, highly refractive large granules. In cresyl blue-Wright preparations they appeared black when the cell was in focus, and as a pink circle when the cell was out of focus. The granules may be confused with oil droplets and highly refractile débris, but these sub-

⁵ Cunningham T Donald. A Method for the Permanent Staining of Reticulated Cells, Arch Int Med 26:405 (Oct) 1920

stances, being on the surface, appeared refractile when the cell was in focus and black when the cell was not in focus. There was usually one to a cell, occasionally two. They were located either within the body of the cell or at its edge. They were frequently recognized free in the plasma in the fresh blood, or as a highly refractile granule within the corpuscles. When on the periphery the granule would adhere to any surface that it touched, giving rise to pear-shaped forms when the granule was single, and spindle-shaped forms when two granules were present, especially in fixed smears. The process could be followed in fresh preparations, sealed with petrolatum. The granules are much smaller than platelets, and are easily differentiated by their nonstaining qualities and high refractivity. With cresyl blue in the fresh, they have a pink reflex. The granules could be mashed from the cells and retained their identity in the serum. These granules are about the size of the granules of eosinophil leukocytes, sometimes slightly smaller. Cells containing these granules were among the last to hemolyze. They frequently showed diffuse basophilia. The granules were recognized in vitally stained normoblasts and in reticulated cells. In the normoblast they have a position by the nucleus suggesting a centrosome-like body or more nearly the centrosphere. Occasionally, in fresh preparations containing a few granules of brilliant cresyl blue, some of the bodies were recognized attached to the red cell by a thin pellicle, which, from its wrinkled character, showed it to be a membrane around the whole red cell, with the intact red cell inside, but separate from the refractive granule. This membrane stained heavily with eosin. The occurrence of these granules suggests young cells rather than degenerative cells. Smears of bone marrow from a young dog showed the refractive granules in 40 per cent of the red cells. They were practically always present in normal blood (less than 1 per cent). Pepper⁶ described granules which apparently corresponded to these, in rabbits' blood, but noted them only after standing from twenty-four to forty-eight hours. In the fresh preparations the granules may be confused with the "knobs" of crenated cells. The "capsule-bodies" described by Schilling-Torgau⁷ in the guinea-pig have some of the characteristics of these refractive granules, although in human and dog blood the structures are smaller than he has pictured the capsule bodies. He considers them related to the Ehrlich-Heinz bodies. In our fresh preparations it seemed evident that the refractive granules were inside the cell.

⁶ Pepper, O H Perry. Observations on the Vitally Stainable Reticulation and Chromatic Granules in Erythrocytes Preserved in Vitro, *Arch Int Med* **30** 801 (Dec) 1922

⁷ Schilling-Torgau, V. Arbeiten über Erythrozyten IV Kapselkörper, Pseudonukleide, Innenkörper usw., sowie die Zentralkornchen Gruppe in Saugetiererythrozyten, *Folia Haematologica*, *Arch Pt 1* **14** 129 (Nov) 1912

proper in the "youngest" cells, and just underneath a limiting membrane at a later stage, and finally quite separated (attached only by a pellicle of this membrane) ultimately becoming dislodged and free. The granules measured about 1 micron in diameter (in fixed preparations). Unlike the Howell-Jolly bodies, they show just as clearly in films stained only with eosin.

2 Similar refractile granules, but much smaller, frequently two or more to a cell, commonly on the periphery, although also found on the interior.

3 Granules as large as the first kind, but nonrefractile and staining blue with cresyl blue-Wright combination, usually single and in the interior of the cell, occasionally two.

4 Granules similar to the foregoing, but much smaller, and frequently two or more.

Owing to the confusion in the naming of intracellular particles in the erythrocytes, it seems wisest to call the granules of Type I highly refractive, intracellular granules, in recognition of their outstanding characteristic. In some respects they can be identified with the Howell-Jolly⁸ bodies, with Heinz⁹ bodies, with the bodies described by Morris¹⁰ as nuclear particles, by Schmauch¹¹ as "endoglobulare Korperchen" and by Schilling-Torgau⁷ as "capsule bodies." These bodies, however, cannot be considered as taking any of the stains, as do the bodies described by these authors, although they appear colored because of the light reflex from their highly refractive substance, the tinge of color being determined by the surrounding color, sometimes similar, sometimes complementary. In this respect they never suggest nuclear particles, having no reaction in common with the nucleus. Their behavior in appearing during certain stages of anemia resembles the granules described by the various authors (Howell, Schmauch), their increase (at one stage) coincident with that of the basophilic granules in the red cells (Morris) is another point of similarity. They differ in being found in normal blood. Cells with refractile granules of Type I within their substance did not agglutinate. The question whether these cells mature in the circulation was studied *in vitro*, but the complicating factor of crenation made both agglutination and staining experiments in dogs difficult and of no conclusive value. In human blood there appeared to be a progressive increase in agglutination, reaching a

⁸ Howell, W H. The Life History of the Formed Elements of the Blood, Especially the Red Blood Corpuscles, *J Morphol* **4** 100 (July) 1890.

⁹ Heinz, R. Morphologische Verenderungen der rothen Blutkorperchen durch Gifte, *Virchows Arch f path Anat* **122** 112 (Oct) 1890.

¹⁰ Morris, Roger S. Nuclear Particles in the Erythrocytes, *Arch Int Med* **3** 93 (March) 1909.

¹¹ Schmauch, G. Ueber endoglobulare Korperchen in den Erythrocyten der Katze, *Virchows Arch f path Anat* **156** 201 (May) 1899.

maximum when the number which was that of the refractive granule cells was reached, after two or three days. This, at least, is suggestive that the cells with reticulum inside may change their properties with age, although, of course, these conditions are quite abnormal.

Dogs that were given transfusions with corpuscles which could be separated by an agglutinating serum and patients who were transfused were followed, comparing the nonagglutinated cell count with the count of cells showing reticulation, nucleation and refractile bodies within the

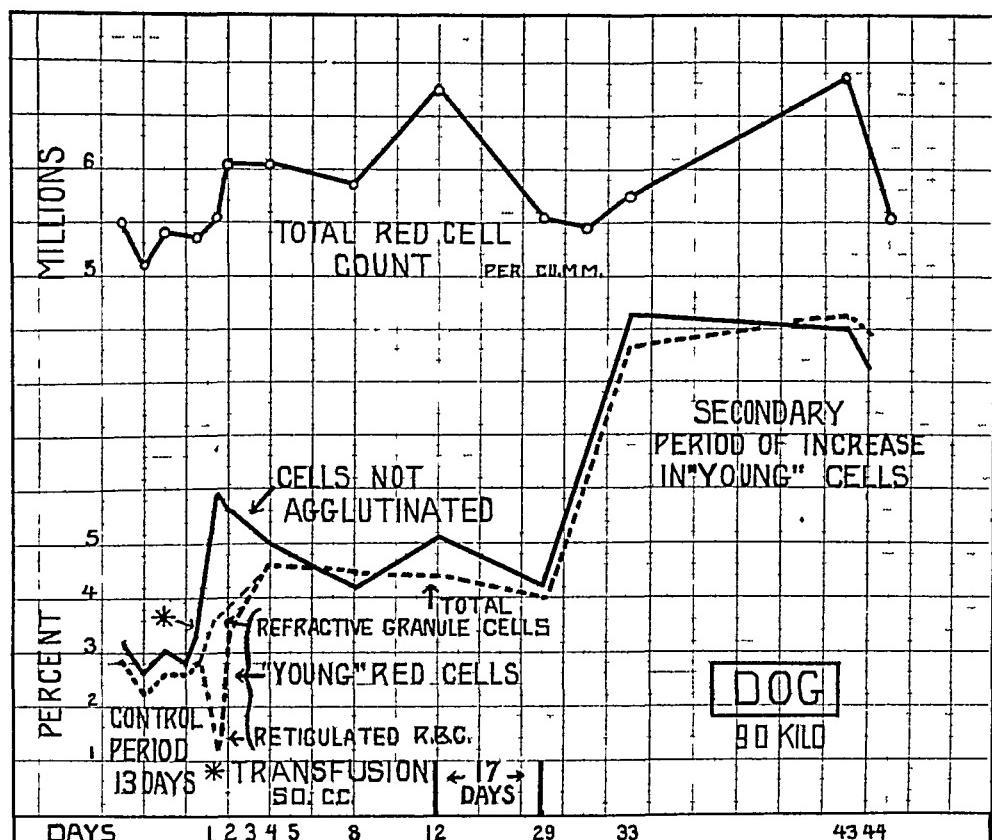


Fig 1.—Showing rise in number of refractive granule red cells and temporary fall in number of reticulated red cells in comparison with the total nonagglutinable cells in a dog receiving 50 cc of compatible blood of a different agglutination type, without previous bleeding. A secondary rise in young and in nonagglutinable cells after thirty-three days.

cell. It was found that immediately after the transfusion (Figs. 1, 4 and 5) the total count of cells showing the reticulum fell, but the number of young cells equaled the number of nonagglutinated cells within from two to four days, and ran parallel after this, so that further counts of nonagglutinated cells could no longer be considered as representing the donor's cells. The donor's blood in most cases contained less than 1 per cent of reticulated cells. Dogs were then bled so that there was

a rise in the number of young cells, a parallel rise in both nonagglutinated and young cells was noted (Fig 2)

Preparations were then made of nontransfused corpuscles and an agglutinating serum, and two series were made—one for making counts of the progress of agglutination and the other for staining to determine the character of the nonagglutinated cells. Figure 3 shows that, while after twenty minutes only 3 per cent of the nonagglutinated cells showed diffuse basophilia, stippling, nuclei, reticulum and refractile

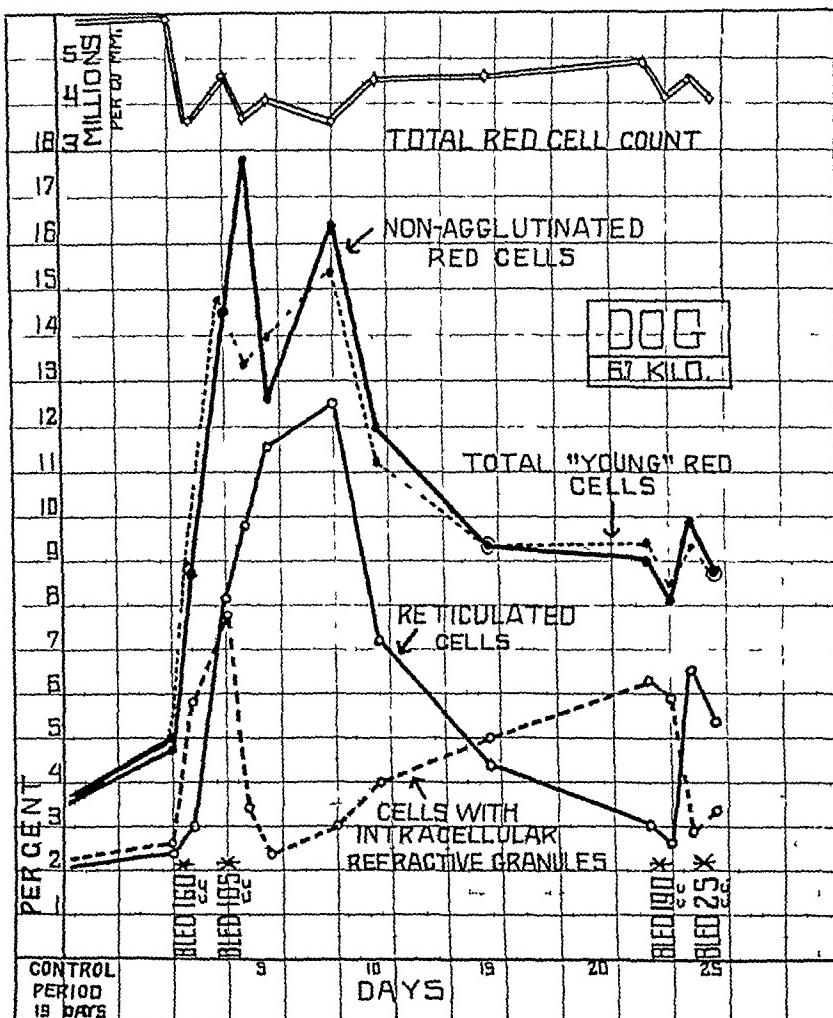


Fig 2.—One of a series of dogs subjected to hemorrhage. A temporary rise in the refractive granule red cells, until the supply is exhausted, is noted after the first hemorrhage, and inverse relation between the refractive granule red cells and reticulated red cells in hemorrhage and recovery is shown. The nucleated red cells remained below 1 per cent. The numerical relation between the "young" cells and the nonagglutinated cells is shown.

bodies within the cell, the proportion rose rapidly until finally 70 per cent of the nonagglutinated cells were of this kind. After this period the reticulum stained as coarse granules in wet preparations. In other words, as the other cells were gradually drawn into the clumps, the cells with basophilic phenomena and refractile bodies remained free

The forms found corresponded to those of fresh preparations, and did not appear to be degenerative effects. In making this test, it is essential to be sure that there is no rouleaux formation, as the reticulated cells are excluded from the rouleaux and give an almost similar picture.

Two human cases were apparent exceptions, in that, although the reticulated count was high, the agglutination was complete. It was found that both patients had a large percentage of macrocytes and megaloblasts, and vital staining with cresyl blue showed that reticulated

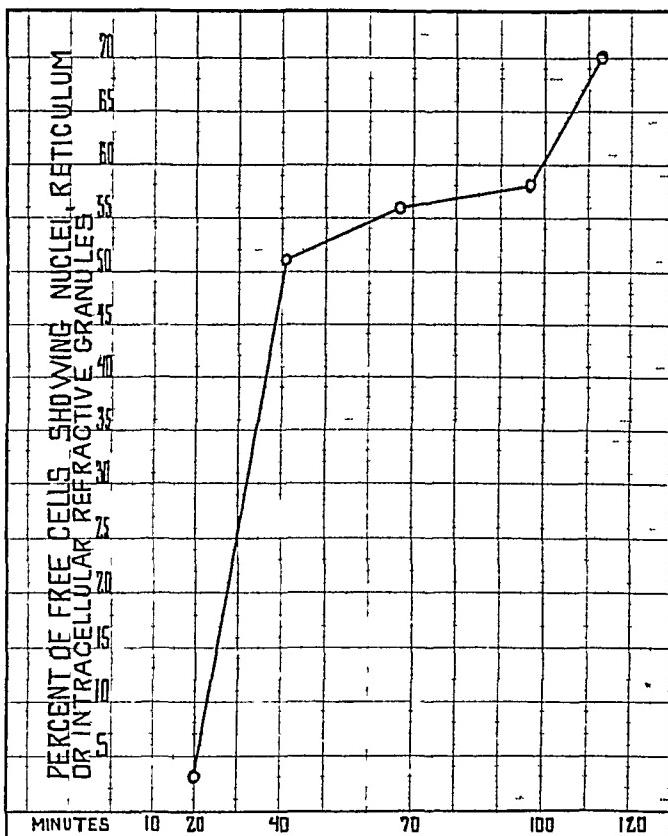


Fig. 3.—One of a series of analyses of the nonagglutinated cells with supravital staining with brilliant cresyl blue. Twenty minutes after mixing the corpuscles of this dog with an agglutinating serum, 3 per cent of the red cells which were not yet agglutinated showed internal bodies of some kind. After two hours, 70 per cent of the few cells which still remained free showed these structures.

macrocyles differ from reticulated normocytes in being included in the agglutinated clumps. Cells in which the refractile bodies were at the periphery were sticky and adhered to the groups.

In normal blood from human beings and dogs, the number of non-agglutinable cells after twenty-four hours was around 1 per cent and ran fairly parallel to the number of cells showing reticulation and refractile bodies within the cell.

The immediate effect of a transfusion of from 65 to 135 cc of blood in an 11 kilogram dog from a dog of the same type and the same breed was an immediate increase in the refractile granule cells and a decrease in the reticulated cells for one or two days, followed by a rise. This was true whether the dogs were bled previously and transfused with the same amount or were given the transfusion without previous bleeding (Fig. 4). The drop in reticulocyte number was similar to that found by Vogel and McCurdy,¹² Robertson¹³ and by Krumbhaar

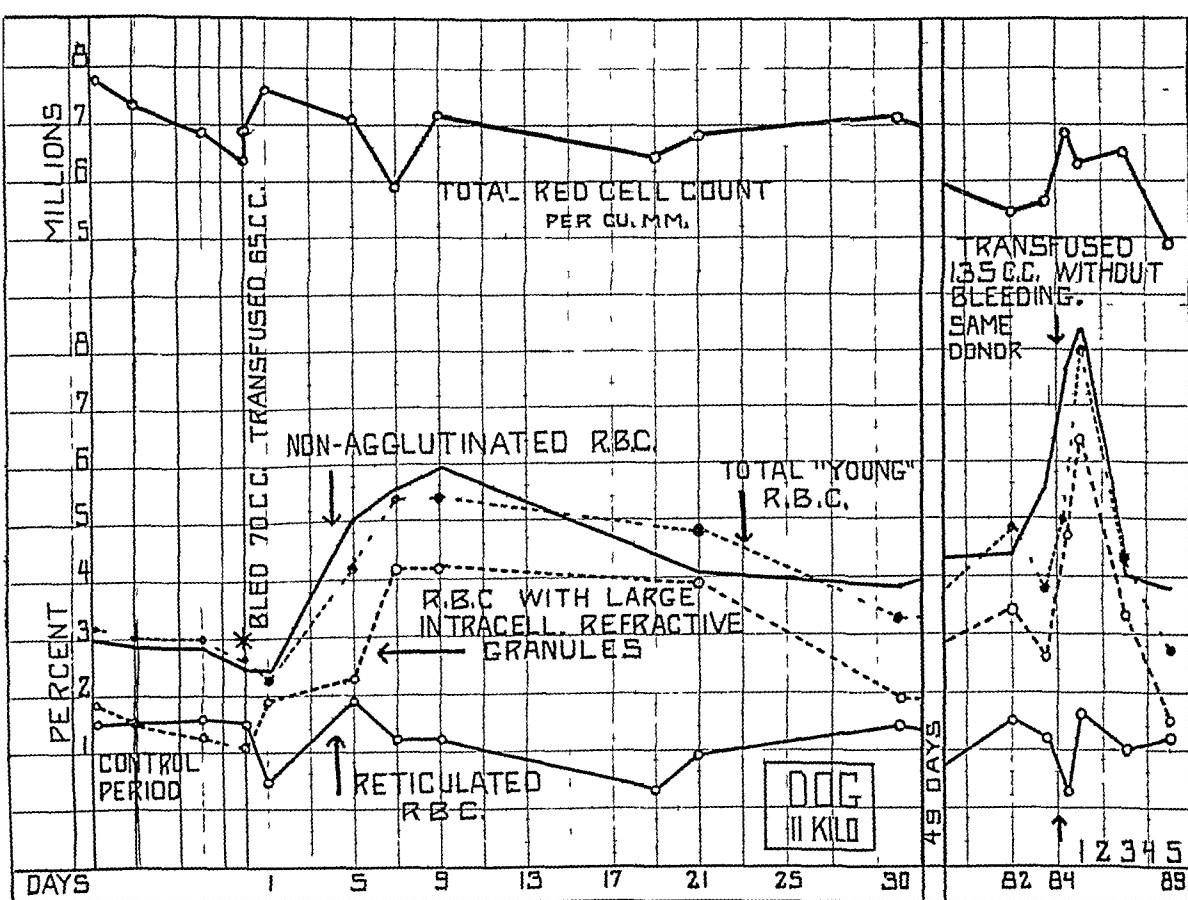


Fig. 4.—One of a series of dogs given transfusions with and without previous bleeding. This dog was transfused with blood of the same agglutination type. The relation of the reticulated red cells, the refractive granule red cells, the total young cells, the nonagglutinable cells and the total red count is shown.

and Chanutin¹⁴ in experimental plethora, but it occurred in animals which had been previously bled and theoretically were not plethoric. The sudden anemias developing in animals that have been previously

12 Vogel, Karl M., and McCurdy, U. F. Blood Transfusion and Regeneration in Pernicious Anaemia, *Arch. Int. Med.* **12** 707 (Dec.) 1913

13 Robertson, Oswald H. The Effects of Experimental Plethora on Blood Production, *J. Exper. Med.* **26** 221 (Aug.) 1917

14 Krumbhaar, E. B., and Chanutin, Alfred. Studies on Experimental Plethora in Dogs and Rabbits, *J. Exper. Med.* **35** 847 (June) 1922

repeatedly transfused (Robertson) was noted in one of our dogs between the twenty-ninth and thirty-second day after a single transfusion (Fig 1). In this case, 50 cc of blood were given to a dog weighing 9 kilograms, without previously bleeding. The rise in reticulated count, and incidentally in the nonagglutinated cells, is shown in Figure 1. The first part of this curve shows the response of the "young" red cells when the bloods are compatible, but of different types, as when a Type II patient is transfused with a Type IV (Moss) blood.

The relation between the number of red cells not agglutinated, the number of cells showing only refractile granules and those cells showing a reticulum (many of which contained refractive granules) after hemorrhage is shown in Figure 2. This was a dog which was subjected to several hemorrhages, without replacement of fluid with salt solution, the number of red cells showing only refractive granules first increased, then decreased, while the reticulocytes increased, but with improvement in the condition, the reticulocytes decreased with increase in the cells showing only refractive granules inside of the cell. In our series of dogs, the increase in normoblasts was slight during any of the experiments, being less than 1 per cent.

Figure 5 shows the response of the immature cells in a case of secondary anemia (mitral stenosis, uterine fibroids). The patient, Type II, received 400 cc of Type IV (Moss) blood. Just after the transfusion, the refractive granule red cells in the circulation increased in number, and began to decrease after the second day, when the reticulated cells began to increase in number. The sum of the two types about equaled the number of the nonagglutinable cells on the fourth day, and ran fairly parallel after that. Figure 5 also shows a case of pernicious anemia in which, after a transfusion of 650 cc, there was a fall in the number of reticulated cells in the peripheral circulation, accompanied by a temporary rise in the number of refractive granule red cells. Here, also, the total number of immature cells equaled the number of nonagglutinable cells after the fourth day, and the numbers ran parallel after that. The difference between the total number of young cells and total number of nonagglutinable cells during the first four days probably represents the foreign cells in the circulation. The types of the nonagglutinated cells, in these and in the other preparations, was determined by supravital staining with cresyl blue, and the examination of the wet preparation sealed with petrolatum.

In the case of pernicious anemia shown in Figure 5, the number of reticulated cells did not show much evidence of activity, although the fact that the total red cell count did not decrease shows that cells were being supplied to the circulation. Evidently during the first eleven days, in this case, the cells matured in the blood-forming organs before

they were discharged into the circulation. Later the more immature cells started to come to the peripheral blood.

In these preparations, the counts of the nonagglutinated cells were the maximum number not agglutinated. This was determined by making repeated counts during the course of three or more hours, and the maximum determined by direct observation.

The relative numbers of the different types of cells in the peripheral circulation was considered as not being dependent on the total blood

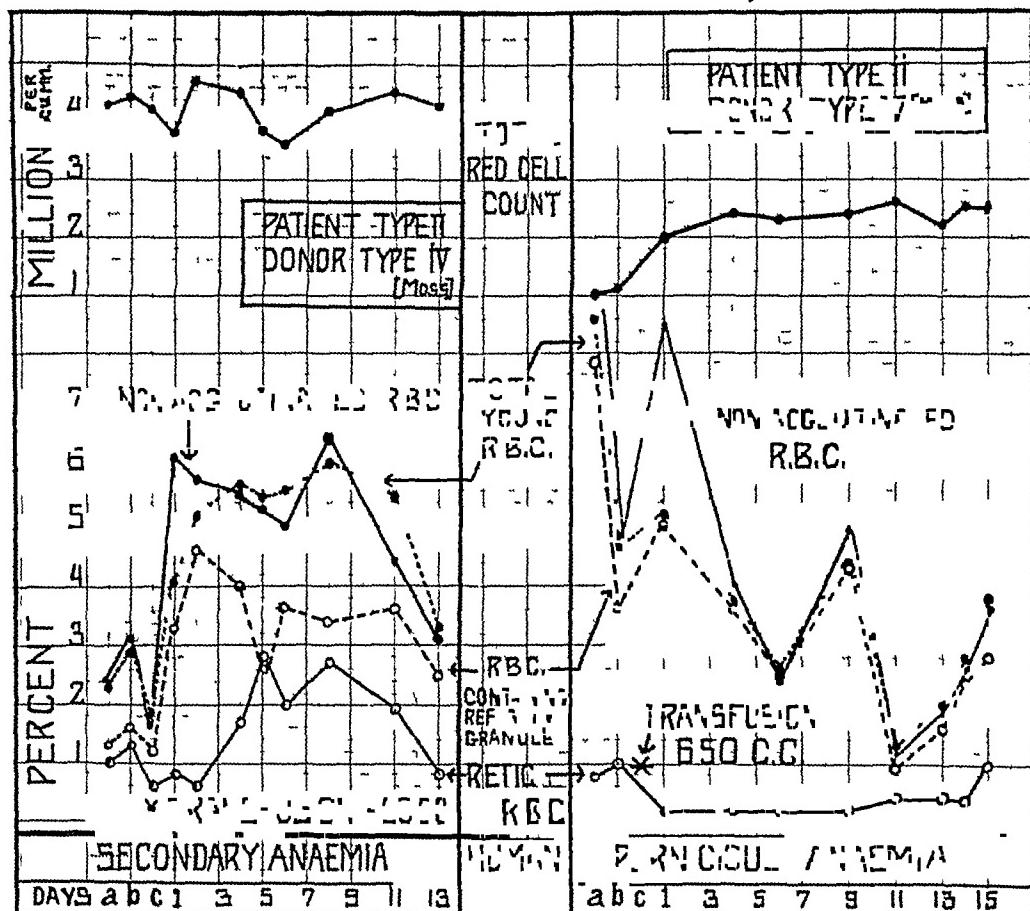


Fig. 5.—Two of a series of patients with anemia. The curves represent individual cases, and the differences have probably no intrinsic significance in the differential diagnosis of the cause of the anemia.

volume, and the latter was not determined in these experiments. The difference in composition of the blood in different parts of the body was not taken into account, as the data are comparative and represent capillary blood taken from the same region for each observation.

COMMENT

The fact that certain red cells—the forms classed as young cells—may not agglutinate with agglutinating serums accounts for the high

counts obtained in some nontransfused persons. It also means that the counts of cells (after the number of cells showing basophilic phenomena and refractive bodies within the cell has reached the number of nonagglutinable cells in a transfused patient) are of little value from the point of view of following the donor's cells. After from two to four days no definite statement can be made as to the persistence of the donor's cells. The counts plotted out in these cases merely show the response of the patient in being able to produce young cells. These cells frequently decreased as the patient's blood count increased in from several weeks to three months in the cases reported. Thus in Case B reported by Wearn, Warren and Ames,² when the blood count reached 4,556,000 (111 days after a transfusion) the percentage of nonagglutinable cells fell to 0.77 per cent.

These observations also offer an explanation of the irregular curves obtained by Ashby,¹⁵ and by Wearn, Warren and Ames² with rises and falls in the number of supposed donor's cells, and explain the fact that after a Type II patient was transfused with Type II blood (Case A, Wearn, Warren and Ames) the nonagglutinable cells rose almost as high as when Type IV (Moss) cells were given, using Type IV serum in both cases to agglutinate the cells (Fig 4, dog experiment).

Ashby recognized the variation in the response to agglutination in nontransfused persons, noting that the counts of "corpuscles lying between clumps is usually from 0.5 to 0.7 per cent of the total blood count, but it may vary in different bloods from 0.03 to 3.4 per cent."

It is interesting to note the difference in the behavior of the reticulated macrocytes and megaloblasts and normocytes and normoblasts. Another differential characteristic was pointed out by Morris and Thayer¹⁶ in the ability of the macrocytes to change their shapes.

The property of nonagglutination is, then, possessed in common by reticulated normocytes, normoblasts, stippled cells, cells with refractive bodies within the cell substance, and is a property of immature red cells. The formation of pointed cells in smears from these cells indicates that all poikilocytosis does not indicate blood destruction, as these cells are among the last to hemolyze.

Key¹⁷ described reticulated cells of the rabbit as having a tendency to agglutinate with each other and to adhere to foreign bodies in the blood, particularly in oxalated blood in hypotonic salt solution. He

15 Ashby, Winifred. The Periodicity in Eliminative Activity Shown by the Organism, *J Exper Med* **34** 127 (Aug) 1921

16 Morris, Roger S., and Thayer, William S. Amoeboid Movements in Macrocytes and Megaloblasts, *Arch Int Med* **8** 581 (Nov) 1911

17 Key, J. Albert. Studies on Erythrocytes with Special Reference to Reticulum, Polychromatophilia and Mitochondria, *Arch Int Med* **28** 511 (Nov) 1921

noted that the reticulated cells had a tendency to rise, being lighter than normal erythrocytes Toward agglutinating serum, however, the behavior appears to be different Whether the specific gravity factor plays much of a part in this separation is questionable

The fact that there was little difference in the response of dogs which had been bled immediately before transfusion and those which were transfused without previous bleeding and in dogs in which the same or a different (but compatible) type of corpuscles were used suggests that the transfused cells last only a short time—a few days at the maximum, and that their rapid disappearance leaves the animal in a potentially anemic condition, "calling out" the production of young cells The "rest" which the marrow has had for a day, together with the improved conditions which the donor's corpuscles bring about while they are present, enables the marrow to respond to a stimulus which, in anemic cases at least, was inadequate before The production of many young cells in animals having presumably the normal number of red cells suggests this view

Boycott and Douglas¹⁸ and also C Drinker, K Drinker and Kreutzmann¹⁹ have pointed out that following a hemorrhage in dogs there is a tendency to over-regeneration, with the eventual production of polycythemia As our studies show that after transfusion the picture becomes much like that after hemorrhage, the "stimulating" effect of transfusions must probably lie in this factor

In response to a "call" for young cells, either after transfusion or after hemorrhage, the first cells to be delivered are those containing the large refractive granules, then the reticulated cells appear in increased amount As these contain refractive granules in many cases, the drop in the number of refractive granule cells (Fig 2) is only apparent Finally, the nucleated red cells increase During recovery, the disappearance or reduction is in inverse order The cells containing only the refractive granules are then the final stage in the maturation of a red cell, and their number in the circulation is a fair indication of the rate of blood production during health (data published elsewhere), and their relative number is of prognostic importance in conditions of blood regeneration An increase in their number, with a decrease in the number of reticulocytes and normoblasts, indicates that conditions are

¹⁸ Boycott, A E, and Douglas, C G On the Carbon Monoxide Method of Determining the Total Oxygen Capacity and Volume of Blood in Animals, with Some Experiments on Anaemia and Transfusion, *J Path & Bacteriol* **13** 275, 1909

¹⁹ Drinker, Cecil K, Drinker, Katherine R, and Kreutzmann, Henry A The Factors Concerned in the Appearance of Nucleated Red Blood Corpuscles in the Peripheral Blood II Influence of Procedures Designed to Increase the Rate of Blood Flow Through the Blood-Forming Organs—Hemorrhage and Infusion, *J Exper Med* **27** 395 (March) 1918

returning to normal, whereas their decrease suggests that cells are being used before maturity or that an aplastic condition is developing, if accompanied by a decrease in the more immature forms.

The resistance to agglutination is probably not due to absence of so-called agglutinogens but to a demonstrable membrane around the immature cell.

These findings are of practical interest in giving an additional laboratory prognostic sign in hemorrhage and anemia and of indicating a possible source of error in assuming that bloods are compatible, whereas in reality the increase in young forms may be the cause of readings of weak agglutination or no agglutination when the compatibility tests are made under other than ideal conditions. It is possible that some reactions, especially in subsequent transfusions, may have their origin in improper readings from this cause.

SUMMARY AND CONCLUSION

For blood of man and dog

1 Reticulated normocytes are not agglutinated by serums that affect the other red corpuscles.

2 Normoblasts and cells containing large highly refractive granules within the cell are not agglutinated.

3 The use of agglutination in recognizing the cells of a donor in a mixture of two bloods in a transfused patient is of little value after the number of young cells reaches the number of nonagglutinable cells, usually in from two to four days.

4 Reticulated macrocytes and megaloblasts do not follow the behavior of the reticulated normocytes toward agglutinating serums.

5 Nonagglutination is a property which is evidently common to immature red cells.

6 Cells showing highly refractile intracellular granules are young cells. Owing to the adhesive nature of the granules when they are peripheral, the cells frequently show pear-shaped or spindle-shaped forms in stained smears.

7 Cells showing only the refractive granules represent the final stage in the production of mature red cells, and their increase, with a decrease in reticulocytes after hemorrhage or hemolysis, indicates a return to normal, whereas their decrease, with an increase in the reticulocytes, is indicative of the continuation of the effects of the disease process.

8 The resistance to agglutination is probably due to a demonstrable membrane around the immature cell.

9 After hemorrhage, the cells showing the large intracellular refractive granules are the first to be delivered into the circulation, then the reticulated cells (many of which contain the granule), and

finally the nucleated red cells Disappearance during recovery is in the reverse order

10 After a transfusion, the process is similar, the effect being that of a potential hemorrhage

11 The reduction of the number of reticulated cells immediately after a transfusion, with an increase in the number of cells showing the refractive intracellular granule, suggests that one of the temporary effects of a transfusion is to allow the forming red cells time to advance one step further in their process of developing into a mature cell The transfusion then does not depress the erythropoietic tissue, but temporarily makes it more normal

ALIMENTARY LEUKOCYTOSIS IN VARIOUS PATHOLOGIC CONDITIONS

A FURTHER STUDY IN REFERENCE TO THE CRISE HEMOCLASIQUE OF VIDAL *

HENRY M FEINBLATT, MD

BROOKLYN

This report is based on the use of the Widal test for hepatic insufficiency in a group of fifty patients with miscellaneous conditions. It represents the second phase of a study suggested to me by the statement by Widal, Abrami and Iancovesco¹ in 1920 that leukopenia following a standard protein meal is to be regarded as a delicate test for insufficiency of the liver.

The technic of the test proposed by Widal is simple. The subject to be examined abstains completely from food for a period of at least five hours preceding the test. This detail is of great importance, as the ingestion of nitrogenous food, no matter how small the amount, interferes greatly with the reaction. A leukocyte count is made, and then the subject drinks 200 gm of milk (a glass of milk, the exact amount not being essential). Subsequently, the leukocytes are counted at intervals of twenty minutes (the author uses half hour intervals) for a period of two hours. Normally, there is a slight leukocytosis following the ingestion of the milk, and the count never falls below the prealimentary level. The occurrence of postalimentary leukopenia is considered pathologic and an evidence of hepatic insufficiency. This leukopenia when present, usually appears in the first hour.

The principal experimental data on which Widal's test is based include the production of a crise hémoclasique (1) by the injection of commercial peptone into the general circulation of a dog, (2) by the establishment of an anastomosis between the portal vein and the inferior vena cava of a dog during the digestive period, under which conditions no crisis occurs in unfed controls, and (3) by the introduction of blood from the portal vein of a dog during the height of the digestive period into the saphenous vein of the same animal. The syndrome of the crise hémoclasique, which is attributed to an upset of the colloidal balance of the blood, is characterized by leukopenia, a fall of blood pressure, hypercoagulability, and a change in the refractive index of the serum. The

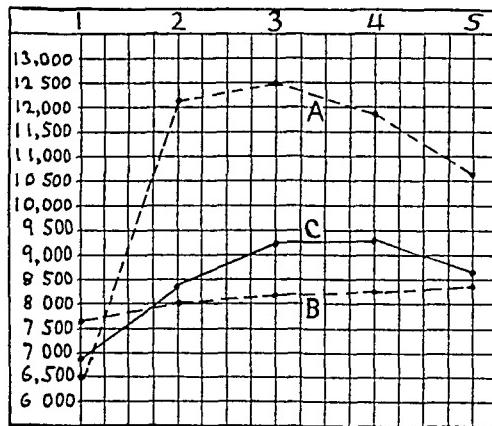
* From the Department of Internal Medicine, Long Island College Hospital, Brooklyn, N Y

1 Widal, F., Abrami, P., and Iancovesco, N. L'Épreuve de l'hémoclasie digestive dans l'étude de l'insuffisance hépatique, Presse med 28 893 (Dec 11) 1920

most important component of the reaction, and the one on which the clinical test is built, is the fall in the leukocyte count

On the basis of his investigations, Widal formulated the hypothesis that one of the functions of the liver, the proteopexic function, is to assist the peptones, proteoses and other disintegrating protein substances found in the portal vein during the digestive period and to transform them into an innocuous form. A deficiency of the proteopexic function allows the entrance of split protein products into the general circulation, causing the disturbance of colloidal balance which is manifested clinically by the phenomena of the hemoclasie crisis.

In a previous communication, the author² reported a study of post-alimentary leukocyte curves in eighty normal persons. In every instance, some degree of leukocytosis followed the consumption of the glass of milk, in other words, the crise hémoclasique, as judged by the



Post-alimentary leukocyte curves in eighty normal persons 1, after five hours' fast and before test meal, 2, one-half hour after milk, 3, one hour after milk, 4, one and one-half hours after milk, 5, two hours after milk, *A*, maximal degree of leukocytosis, *B*, minimal degree, *C*, composite curve of leukocytosis in eighty normal persons. In every instance, some degree of leukocytosis was observed. The interrupted lines *A* and *B* represent the limits of variation, that is, they are the curves of the cases in which the maximal and the minimal degrees of leukocytosis, respectively, occurred. The solid line *C* represents the composite curve of normal post-alimentary leukocytosis, the average of the curves obtained.

post-alimentary leukocyte curve, did not once occur in a normal person. There was considerable uniformity in the curves. The chart shows the composite curve given by these eighty normal subjects, together with the two extreme variants.

The literature appertaining to digestive hemoclasie is voluminous and, to a large extent, contradictory, and it would be an unprofitable

² Feinblatt, H. M. Alimentary Leukocytosis in Eighty Normal Men. A Study in Reference to the Crise Hémoclasique of Widal, J. A. M. A. 80: 613 (March 3) 1923.

task to review it. In general, French authors find the test of value in the differentiation of conditions affecting the intestinal tube and its appendages, and they appear to have established the fact that the crise hémoclasique disappears with the removal of its cause. For example, digestive hemoclasis is consistently associated with cholelithiasis, but disappears a month or so after removal of the gallbladder. Other workers, particularly in Germany, fail to obtain consistent results with this test.

TABLE 1—*Cases Yielding a Typical Crise Hémoclasique*

No	Sex	Age	Clinical Diagnosis	After 200 Gm of Milk			
				Before Milk	½ Hour	1 Hour	1½ Hours
1	F	38	Bronchial asthma	8,600	8,400	8,000	7,200
2	M	50	Laennec's cirrhosis	4,000	2,800	2,800	1,600
3	M	38	Cholelithiasis	10,000	7,600	5,200	6,000
4	M	35	Syphilis of liver, ascites	8,000	7,200	7,200	6,500
5	M	24	Idiosyncrasy to milk, sick with nausea, apparently due to test meal	12,400	10,400	8,450	
6	M	42	Laennec's cirrhosis, bronchitis	20,000	15,400	11,200	
7	M	25	Bronchial asthma, positive skin reactions to many food proteins	12,600	12,400	10,000	11,000
8	F	25	Hay fever, sensitive to ragweed goldenrod and rye	11,200	10,600	8,200	8,600
9	M	30	Chronic otitis media, took ½ grain calomel on day preceding test	10,000	7,000	6,200	10,000
10	F	48	Passive congestion of liver, auricular fibrillation	10,400	6,800	7,200	13,000
11	F	33	Mitral stenosis	7,400	5,600	7,000	7,800
12	M	23	Arthritis of ankle	11,800	9,200	11,000	12,400
13	M	62	Chronic alcoholism	8,000	7,000	6,400	6,600
14	M	53	Bronchial asthma	9,200	5,800	11,800	13,000
15	M	64	Sciatica, pleurisy	8,200	5,800	6,400	7,400
16	M	62	Pneumonia, jaundice	24,000	24,000	19,800	23,000
17	M	62	Pneumonia, jaundice	37,400	27,600	24,200	41,400
18	F	42	Arthritis deformans	10,600	8,000	9,000	11,000
19	M	13	Essential epilepsy	6,000	6,000	5,800	5,900
20	M	46	Arthritis deformans	7,900	6,600	6,600	6,400
21	M	44	Neurocirculatory asthenia	5,000	4,400	3,800	5,400
22	F	42	Bronchial asthma, all skin tests negative	11,600	11,600	8,400	8,800

SCOPE OF THIS STUDY

The object of this investigation was not specifically to study the Widal test with reference to insufficiencies of the liver, but to examine a miscellaneous group of patients in the hope that leads for further study might thus be furnished. The fact that in a consecutive series of eighty normal persons a crise hémoclasique did not once occur establishes the fact that this phenomenon must necessarily be construed as pathologic, but, depending, as it does, on an upset of the colloidal balance of the blood, the crisis might conceivably result from a great variety of abnormal states.

The Widal test was performed on fifty patients suffering from various conditions. According to the type of postalimentary leukocyte curve attained, the patients were classified into three groups as follows: (1) those yielding a frank crise hémoclasique (relative leukopenia one-

half and one hour after the test meal), (2) those yielding a normal curve (relative leukocytosis one-half and one hour after the test meal), and (3) those yielding an indeterminate curve.

The data presented in the foregoing tables are sufficient to show that the hemoclastic crisis may occur in a great variety of conditions in which hepatic insufficiency is not evident on clinical examination. These

TABLE 2—*Cases Yielding a Normal Response in Postalimentary Leukocytosis*

No	Sex	Age	Clinical Diagnosis	After 200 Gm of Milk			
				Before Milk	½ Hour	1 Hour	1½ Hours
1	M	23	Essential epilepsy	11,800	12,600	13,000	15,200
2	M	13	Familial epilepsy	10,800	11,400	14,000	14,200
3	F	24	Mitral stenosis with decompensation, pregnancy	7,400	11,400	9,200	8,600
4	F	48	Arthritis deformans, pulmonary tuberculosis, old carcinoma of breast	7,400	7,800	8,000	8,400
5	F	49	Carcinoma of bronchus	6,600	8,000	10,000	9,400
6	F	50	Hyperthyroidism, myocarditis	7,400	7,600	10,000	8,000
7	F	22	Toxic polyneuritis	6,600	9,000	9,400	7,800
8	F	39	Chlorosis	7,400	8,600	8,200	9,000
9	M	21	Malaria	4,800	6,200	7,600	7,600
10	M	55	Gastric ulcer	7,200	7,200	8,200	7,400
11	M	55	Chronic glomerular nephritis	7,200	8,600	9,200	6,400
12	M	21	Diabetes mellitus	9,600	11,200	9,200	13,200
13	M	39	Syphilitic arthritis	9,800	10,400	11,000	9,000
14	M	32	Arthritis	8,000	9,000	8,200	9,000
15	M	45	Raynaud's disease	8,000	8,000	10,400	9,800
16	F	32	Trichinosis	12,000	17,600	11,800	11,600

TABLE 3—*Cases Yielding an Indeterminate Curve*

No	Sex	Age	Clinical Diagnosis	After 200 Gm of Milk			
				Before Milk	½ Hour	1 Hour	1½ Hours
1	M	27	Bronchial asthma	9,000	10,000	6,400	7,000
2	M	60	Aortic insufficiency	12,700	11,800	15,000	15,600
3	M	40	Hodgkin's disease	8,100	9,400	7,200	10,200
4	M	68	Uremia, chronic myocarditis	8,200	9,600	7,400	8,400
5	M	55	Passive congestion of liver, cardiac decompensation	8,600	8,800	8,400	9,600
6	M	43	Cardiac decompensation, hydrothorax and enormously enlarged liver	10,400	10,800	8,000	9,000
7	M	60	Pernicious anemia	3,000	3,200	2,500	2,950
8	F	38	Brain tumor	9,400	9,000	9,000	9,000
9	F	45	Diabetes mellitus, hypothyroidism	8,200	8,400	8,000	8,000
10	F	37	Hypothyroidism	8,400	8,200	8,800	7,600
11	M	53	Urticaria	6,600	6,000	10,800	8,000
12	M	47	Perihepatitis	9,720	10,340	8,260	8,600

results, of course, have no great bearing on the validity of the Widal test. In the first place, a considerable degree of anatomic damage to the liver can escape detection by clinical methods, and in the second place, the crisis is supposed to be due to a functional defect of the liver, which would be not in the least incompatible with an organ showing no lesions at necropsy. This test is based entirely on biologic principles. The hemoclastic crisis is evidently a nonspecific anaphylactic reaction, which experimental evidence has shown can be produced by the entrance of portal blood into the general circulation and can be prevented by the

action of the liver on such blood. It is unfair to apply anatomic standards to such a test, except so far as it must be acknowledged that deficiency of function is much more apt to be present in an organ badly damaged.

Many workers, particularly in Germany, having obtained results similar to mine, that is, a hemoclasic crisis in conditions not related to the liver, have been inclined to discredit the whole test. To me this attitude does not appear justified. It undoubtedly is fair to conclude from the evidence that a positive crisis does not necessarily mean that the liver is badly damaged, especially in view of the fact that in certain diseases of the digestive tube and its appendages, for example in cholelithiasis, the hemoclasic reaction disappears with the removal of the cause. Furthermore, the crisis can in no sense be construed as indi-

TABLE 4.—*Summary of Clinical Diagnosis in Twenty-Two Patients Showing the Crise Hemoclasique*

Bronchial asthma	4
Laennec's cirrhosis	2
Arthritis deformans	2
Pneumonia with jaundice	2
Cholelithiasis	1
Syphilis of liver with ascites	1
Idiosyncrasy to milk	1
Hay fever	1
Otitis media (calomel ?)	1
Passive congestion of liver, auricular fibrillation	1
Mitral stenosis	1
Arthritis of ankle	1
Alcoholism	1
Sciatica and pleurisy	1
Essential epilepsy	1
Neurocirculatory asthenia	1
Total	22

cative of a general reduction of hepatic function, but rather of a deficiency of one particular function, the proteopexic function. It is for this reason that it would be a fruitless task to make a parallel study between the Widal test and other tests of liver function, such as the phenoltetrachlorphthalein method.

In two cases in which the patients, both of whom appeared clinically to be suffering from advanced hepatic disease, came to necropsy, the Widal test was of value in the differential diagnosis.

REPORT OF CASES

CASE 1.—J. A., a man, aged 59, married, whose history, physical signs and laboratory findings established the diagnosis of taboparesis, further exhibited considerable enlargement of the abdomen together with the signs of ascites. Paracentesis yielded a thick, mucilaginous fluid, which contained 0.2 gm of albumin per liter, was sterile, and showed a few polymorphonuclear and many undifferentiated cells. The Widal test gave a curve of 10,000 cells before the ingestion of milk, and 10,000, 12,000 and 13,000 cells, respectively, at one-half hour intervals afterwards, that is a normal response. At necropsy the cause

of the ascites was found to be a myxoma involving the omentum and the intestines Except for slight congestion and amyloid change, the liver was normal

CASE 2—T J, a man, aged 53, married, who gave a history of a syphilitic infection eighteen years prior to admission, had suffered for a period of one year from occasional vomiting, followed in the course of several months by weakness, a tremor of the hands, loss of appetite, and, a few days before admission, by jaundice He had always been a heavy drinker On physical examination, the liver could be palpated four fingerbreadths below the costal margin, there was a definite yellowish tinge to the sclerae The Widal test gave a curve of 22,400 cells before the ingestion of milk, and 15,800 and 11,800 cells respectively at one-half hour intervals afterward, that is, a frank hemoclasic crisis The patient died of a hypostatic pneumonia Necropsy revealed evidence of advanced hepatic damage Sections from the liver, which was markedly enlarged, showed considerable perilobular and intralobular fibrosis, with marked regeneration and reduplication of the smaller bile ducts The lobules were irregular in contour, and the majority of them showed fatty infiltration

THE VARIABILITY OF THE LEUKOCYTE CURVE

One point which becomes apparent from an examination of the tabulation seems to be of great practical importance, namely, the variability of the leukocyte curve It appears that the relation of the white blood cell count to the digestive phases will have to receive greater emphasis So marked are the fluctuations which may follow nothing more than the ingestion of a glass of milk that our clinical deductions may often prove to be erroneous unless we make proper allowances Thus one patient, a man, aged 62, with lobar pneumonia, yielded a count of 37,400 cells before ingestion of milk and of 27,600, 24,200 and 41,400 cells, respectively, at one-half intervals afterward Certainly a variation of 17,200 cells in the short space of one-half hour might lead to a different interpretation one way or the other in cases in which only a single specimen is taken It may, perhaps, prove eventually to be more reliable to make our inferences from a leukocyte curve rather than from a single count

CONCLUSIONS

1 The crise hémoclasique of Widal, as evidenced by the postalimentary leukocyte curve, does not occur in normal subjects

2 The hemoclasic crisis has been observed by many workers in patients who showed no clinical evidence of hepatic disease My results have been in accord with this general trend It appears established that this test can in no way be used to measure quantitatively gross organic damage to the liver

3 The Widal test should be considered as relating not to liver function in general, but to one particular liver function, the proteopexic function

4 The proteopexic function is deficient when there is gross organic damage to the liver, frequently it is deficient when there is no other evidence on which to indict the liver

5 The interpretation which should be placed on a positive crise hemoclasique is that it indicates a functional defect of the liver, perhaps transitory, which gives rise to a nonspecific anaphylactic reaction

6 Protein ingestion may give rise to marked oscillations in the leukocyte count. In one patient with pneumonia, there was a variation of 17,200 cells in half an hour. In interpreting the white blood cell count, the influence of the phases of digestion must be accorded proper consideration

616 Carlton Avenue

BLOOD AND PLASMA VOLUME IN OBESITY

GEORGE E BROWN, M D

AND

NORMAN M KEITH, M D

ROCHESTER, MINN

Few estimations of blood volume have been made on obese persons, but those obtained have indicated a small blood volume in comparison with body weight Haldane and Smith¹ were the first to draw attention to this fact Latei Keith, Rowntree and Geraghty² showed that both the blood and plasma volumes were small in certain obese patients Rasmussen and Rasmussen³ compared the blood volume in the wood-chuck in midsummer, just before and during hibernation, and found that there was a relative reduction in blood volume when a maximum amount of fat was stored within the body Our observations on a series of obese patients have confirmed this relationship between blood volume and excessive deposits of fatty tissue In the present series, patients were also studied after they had lost a known amount of weight, chiefly to determine whether loss of weight brought about constant changes in blood and plasma volumes Fourteen cases were followed over a period of several weeks, volumetric studies being made before reduction and following a loss of from 5 to 15 kg in weight The results revealed interesting facts concerning the relationship between blood and plasma volume and obesity, and are reported here

TECHNIC EMPLOYED

The total circulating volume of blood and plasma was determined by the dye method of Keith, Rowntree and Geraghty Vital red and Congo red were both used and gave equally satisfactory results Harris⁴ found that Congo red leaves the blood vessels of cats and dogs less rapidly than does vital red This has not been our experience in dogs or man Our findings with both dyes have given comparable results

1 Haldane, J., and Smith, J L The Mass and Oxygen Capacity of the Blood in Man, *J Physiol* **25** 331-343, 1900

2 Keith, N M , Rowntree, L G , and Geraghty, J T A Method for the Determination of Plasma and Blood Volume, *Arch Int Med* **16** 547-576 (Oct) 1915

3 Rasmussen, A , and Rasmussen, G B The Volume of the Blood During Hibernation and Other Periods of the Year in the Woodchuck (Marmota Monax), *Am J Physiol* **44** 132-148, 1917

4 Harris, D T The Value of the Vital-Red Method as a Clinical Means for the Estimation of the Volume of the Blood, *Brit J Exper Path* **1** 142-158, 1920

well within the possible errors inherent in the method itself. Table 1 shows these comparable results, employing both dyes, in two normal dogs and two patients with mild chronic arthritis. Hematocrit determinations were made by centrifuging 15 cc of blood in calibrated centrifuge tubes for twenty minutes at the rate of 3,000 revolutions a minute. One hundredth of a gram of dry sodium oxalate was used to prevent clotting. The hemoglobin content was estimated according to the Palmer⁵ modification of the Haldane carbon monoxid method. The surface area of these patients was computed from the height and weight formula of Du Bois⁶.

REDUCTION OF WEIGHT

A fairly standardized regimen for reducing weight was used in this series of patients. Average diets of 1,200 calories were given, and

TABLE 1.—*Plasma and Total Blood Volume Estimations by Vital Red and Congo Red Methods*

	Date	Dye Used	Weight, Kg	Plasma Volume, Cc	Plasma Volume, Cc for Each Kg	Blood Volume, Cc	Blood Volume, Cc for Each Kg
Dog B	1/15/21	Congo red	8.6	470	54.6	885	103.0
	1/27/21	Vital red		480		800	
	2/11/21	Vital red	8.0	440	55.0	770	96.5
	2/14/21	Congo red	7.8	495	63.6	850	108.8
Dog W	2/3/21	Congo red	9.7	490	50.3	855	88.0
	2/11/21	Vital red	8.6	440	51.4	760	87.0
	2/14/21	Congo red	7.9	450	55.7	760	96.0
A426051	5/26/23	Congo red	73.0	3,325	45.0	5,750	78.0
	5/29/23	Vital red	73.0	3,300	46.0	5,655	77.0
A426243	6/6/23	Congo red	62.0	3,725	60.0	5,825	91.0
	6/9/23	Vital red	60.0	3,725	62.0	5,825	97.0

fluids were restricted to 1,500 cc. Moderate exercise was taken in the form of walking one or two miles daily. Desiccated thyroid was given by mouth in sufficient dosage to elevate and maintain the metabolic rate at from 20 to 25 per cent above normal for from five to ten days. At this level toxic symptoms were absent or slight. From one to three courses of thyroid treatment as noted above were given each month.

RESULTS

The changes in hemoglobin, red blood corpuscle content, plasma and total blood volume following reduction in weight and surface area varied with the individual case. The detailed findings are given in Table 2.

5 Palmer, W. W. The Colorimetric Determination of Hemoglobin, J. Biol. Chem. 33: 119-126, 1918.

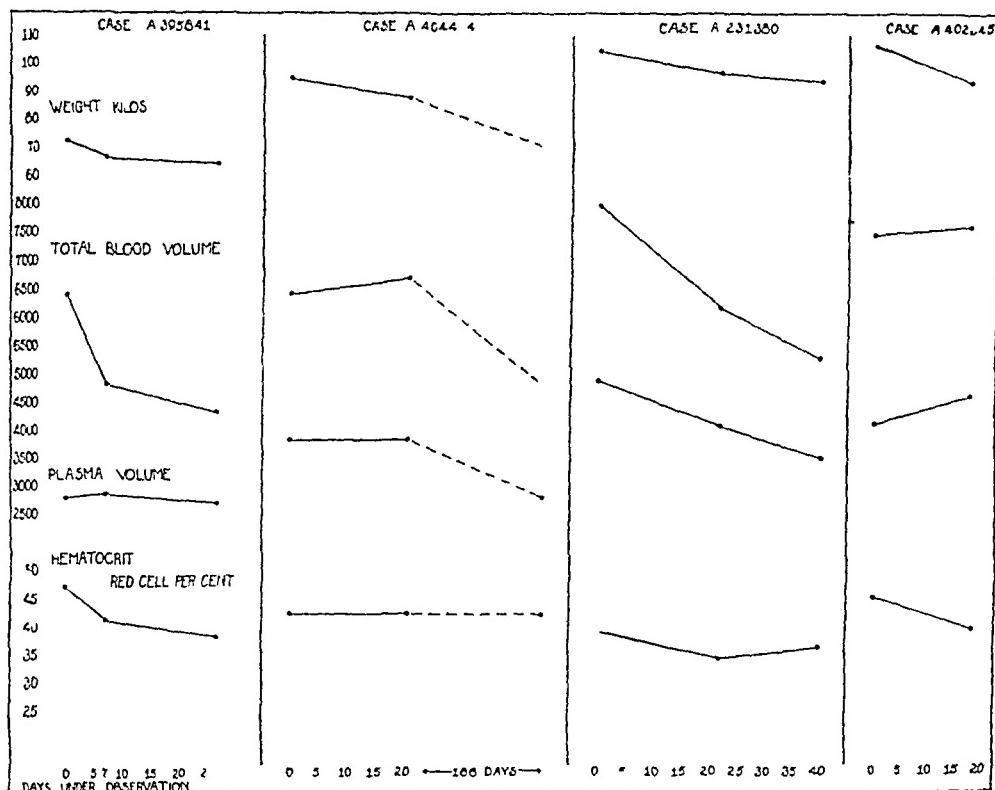
6 Du Bois, D., and Du Bois, E. F. A Formula to Estimate the Approximate Surface Area if Height and Weight be Known. Clinical Calorimetry, Tenth Paper, Arch. Int. Med. 17: 863-871 (June) 1916.

TABLE 2—*Blood Values During Weight Loss (Observations on Fourteen Patients)*

Case	Date	Sex and Age	Weight, Kg	Loss of Wt., Kg	Height, Cm	Surface Area, Sq M	Hemoglobin, per Cent	Hematocrit Erythrocytes, per Cent	Plasma Volume			Whole Blood			Clinical Diagnosis
									Total, Cc	Cc for Each Kg	Cc for Each Sq M	Total, Cc	Cc for Each Kg	Cc for Each Sq M	
1 (A385580)	5/10/22 5/29/22	F 49	106 100	6	162	2.07	82	36	3,750	35	1,810	5,800	55	2,835	Obesity, mild chronic arthritis
2 (A390802)	5/15/22 6/12/22	F 55	99 93	6	167	2.08	110	46	3,620	36	1,740	6,700	67	3,220	Obesity, mild chronic arthritis, mild hypertension
3 (A392006)	5/31/22 6/2/22	M 65	115 111	10	178	2.38	104	41	4,445	38	1,865	7,530	64	2,515	Obesity, myocardial degeneration, arteriosclerosis, edema
4 (A270002)	6/5/22 6/17/22	M 39	104 97	7	167	2.1	108	42	4,500	41	1,950	7,700	70	3,350	On admission, 6/5/22 phlebotomy 600 cc
5 (A402345)	8/25/22 9/12/22	F 14	105 93	12	170	1.86	107	45	4,090	39	2,210	7,485	70	4,020	Obesity, myocardial degeneration, hypertension, arteriosclerosis
6 (A103665)	9/14/22 9/27/22	F 55	87 83	4	157	1.86	101	43	3,365	38	1,810	5,900	67	3,170	Obesity, hypertension, arteriosclerosis
7 (A395121)	6/23/22 7/10/22	M 48	96 88	12	172	2.08	100	47	3,365	35	1,610	6,345	66	3,050	Obesity, cholecystitis
8 (A305811)	7/5/22 7/12/22	F 8/2/22	72 66	8	147	1.64	129	47	2,770	38	1,670	5,900	82	3,000	Acute obesity, ovarian dysfunction
9 (A100920)	8/17/22 9/1/22	F 52	111 96	15	155	2.10	105	44	4,045	36	1,920	7,220	65	3,439	Obesity, hypertension
10 (A101705)	8/21/22 8/31/22	F 15	81 74	7	158	1.8	98	40	3,960	48	2,200	6,710	82	3,730	Obesity, chronic arthritis, mild diabetes
11 (A101451)	9/19/22 10/10/22	F 4/18/23	94 70	7	172	2.06	111	42	3,870	41	1,880	6,450	68	3,430	Obesity, mild hypertension, cholecystitis (?)
12 (A303505)	6/10/22 6/26/22	M 52	115 106	9	172	2.26	116	40	3,830	44	1,925	6,690	77	3,320	Obesity, hypertension
13 (A104776)	5/17/22 5/31/22	F 53	110 131	6	158	2.25	111	41	3,850	27.5	1,640	6,500	47	2,765	Obesity, hypertension
14 (A201380)	5/30/22 6/22/22	M 10	104 96	11	178	2.2	94	39	4,865	47	2,220	7,975	77	3,625	Typhoid fever, obesity
	7/10/22								3,410	37	1,670	5,372	58	2,560	

Percentage of Hemoglobin and Red Blood Corpuscles (Hematocrit)

—The initial determinations for hemoglobin varied from 82 to 129 per cent and for red blood corpuscles, from 36 to 47 per cent. These findings fall within the normal range for both sexes between 30 and 65 years of age. In six of the present series of cases (Cases 2, 5, 6, 7, 8 and 14) there was a distinct, though not marked, fall in the hemoglobin or red blood corpuscle percentage, or in both, following loss of body weight. In the first four of the foregoing cases there was no other evidence of a developing anemia. The patient in Case 14 passed



Four types of variations in blood and plasma volumes during weight reduction

through the typical course of typhoid fever, which might account for a mild degree of secondary anemia. In Case 8 the fall in hemoglobin from 129 to 108 per cent was accompanied by a decrease in the total number of circulating red blood corpuscles, this was probably a true anemia as there was no change in the plasma volume. In the remaining eight cases there were no noticeable changes from the initial determinations.

Plasma Volume—The initial determinations were relatively lower than normal when compared to body weight. In normal persons, the variation is from 42 to 54 cc for each kilogram, in these cases it was

from 27.5 to 48 cc. However, when compared with surface area, the initial plasma volume showed little change from normal.

In Cases 1, 4, 5, 6 and 7, following a reduction in weight of from 4 to 12 kg., there was a definite rise in the total and relative amounts of plasma volume. The relative increase applied to both weight and surface area. In Cases 1 and 4, there was no associated change in percentage of red blood corpuscles, while in three (Cases 5, 6 and 7), there was a measurable fall without other evidences of anemia.

A marked fall (28 to 29 per cent) in total plasma volume occurred in Cases 11 and 14. The histories of these patients are of striking interest. In Case 14, the patient entered the hospital with typhoid fever, which ran a typical course without complications. He lost 11 kg. in weight. Blood examination on three occasions at intervals of three weeks showed a steady decrease in total plasma, amounting in all to 1,424 cc., or 29 per cent, and accompanied by a small decrease in the percentage of red blood corpuscles (from 39 to 36 per cent). The relative decrease in plasma was from 47 to 37 cc. for each kg., and from 2,215 to 1,670 cc. for each square meter. In Case 11, the patient lost 7 kg. in three weeks, and 24 kg. in seven months under strict treatment for obesity. This marked loss in weight was accompanied by a decrease of 1,100 cc., or 28 per cent, in total plasma. The relation of total plasma to body weight, 42 cc. for each kilogram, remained unchanged, but there was a definite decrease in the relative amount of plasma to surface area. There was no striking loss of hemoglobin or change in red blood corpuscle percentage.

In six of the seven remaining cases in which the loss of weight was from 6 to 15 kg., the changes in total and relative plasma volume were small.

Blood Volume.—The initial determinations in all but three cases showed a reduced blood volume when compared to body weight. In these exceptions (Cases 8, 10 and 14), the findings were from 77 to 83 cc. for each kilogram, coming within the range of the normal variation of from 74 to 99 cc. for each kilogram. The variations in the relationship of blood volume to surface area are greater in obese persons than in normal subjects. The former vary from 2,515 to 3,730 cc. for each square meter, and the latter from 2,790 to 3,460 cc. for each square meter. The results of total blood volume estimations were more variable when compared with loss of weight than those of plasma.

Three patients (Cases 1, 4 and 7), after the loss of weight, had an increase in total and relative blood volume, and this was always associated with an increase in the total and relative amount of plasma. The red blood corpuscle percentage did not change in Cases 1 and 4, in Case 7 there was a definite decrease. In Cases 2, 3, 8, 9, 10, 11 and

14, there was a demonstrable decrease in total blood volume, accompanied by no change or a slight fall in the percentage of red blood corpuscles. In five of these (Cases 2, 3, 9, 10 and 11), this decrease in total blood volume was not accompanied by a relative parallel decrease in relation to body weight and surface area. On the contrary, in two, a decrease was found. The latter cases (Cases 14 and 8) were striking on account of a marked fall of from 28 to 29 per cent in blood volume. This decrease was due to a loss of both plasma and red cells in Case 14, while in Case 8 the loss was demonstrable in the red cells only.

In Cases 12 and 13, there was practically no change in total or relative amounts of blood volume. Plasma determinations also showed no change. Both patients lost relatively little weight while under observation.

COMMENT

Loss of weight in this series of obese subjects did not occasion constant changes in blood and plasma volume, or in the percentage of hemoglobin or red blood corpuscles. Four types of blood changes are shown in the chart. In Cases 5, 6 and 7 there was an increase in total plasma, a decrease in the percentage of red blood corpuscles and little or no change in total blood volume. The increase in circulating plasma may be related to the therapeutic use of thyroid extract. In only two cases (Cases 14 and 11) was there a marked decrease in total plasma. In Case 14, typhoid fever was present, and in Case 11, the loss of weight amounted to 24 kg. Loss of plasma in typhoid fever suggests that there may be a similar loss of plasma in other acute febrile diseases. In Case 11, the loss of plasma varied directly with the loss of weight, so that the initial relationship between body weight, total plasma and total blood remained constant 42 and 68 cc for each kilogram. If a low relative blood and plasma volume is always found in obese persons, as our results show, then the determinations in Case 11 indicate that even at the reduced weight of 70 kg the patient had an abnormal amount of adipose tissue.

The total circulating blood was increased in two cases, suggesting that loss of weight may have opened up resting capillaries and thus increased the amount of blood in circulation. In Case 4, the early disappearance of a slight edema may have been a factor in causing an increase in circulating blood volume. The marked decrease in blood volume that occurred in Cases 8 and 14 is of special interest. In Case 8, in which marked obesity developed in six months, the decrease was due to a loss or possible redistribution of red blood corpuscles, as no change was found in the amount of circulating plasma. The fall in red blood corpuscles and hemoglobin percentage strongly indicates that red blood cell destruction had occurred. There were no other clinical

facts indicative of anemia. On the other hand, in Case 14 the red blood corpuscle percentage and total circulating blood volume were decreased, as well as the total plasma. The anemia which occurs in typhoid fever may explain the red cell loss, while the loss of plasma was possibly associated with the excessive protein catabolism present in this disease.

SUMMARY

- 1 The circulating blood and plasma volumes when compared to body weight are smaller in obese than in normal persons.
- 2 Loss of weight in obese subjects, as brought about in this series of cases, did not result in constant changes in blood and plasma volume or in the percentage of hemoglobin or red blood corpuscles (hematocrit).
- 3 In three cases, following loss of weight there was evidence of blood dilution, but no definite evidence of anemia.
- 4 A decrease or increase of total circulating blood volume may occur with reduction in weight. In this series, when a marked decrease occurred, there was evidence of anemia.

MERCURIC CHLORID POISONING *

H B WEISS, M D

CINCINNATI

The most trying group of poisoned patients encountered at a general hospital is the group that has taken mercuric chlorid. It is taken with suicidal intent in over 90 per cent of the instances, and the vast majority of the group are young women. The accidental poisonings are infrequent, and occur when a tablet is taken by mistake for a coal tar or other preparation. Occasionally, the patient who has used the solid tablet in the vagina will present herself. Once a child who had swallowed the mercury from a broken thermometer came under treatment. For the most part, the poison is taken by mouth, usually by swallowing the tablets, and occasionally by dissolving them in water before swallowing. One patient ate some diluted mercurial ointment, and another drank a 1:10 mercuric chlorid solution which she obtained in a hospital.

When the mercury, even in tablet form, enters the stomach, the poison is quickly taken up, and in experimental animals (dogs) the mercury has been detected in the blood three minutes after a tablet was placed in the animal's stomach.¹ This occurred when the dose of mercuric chlorid was 0.5 gm per kilogram of body weight. In doses as small as 0.024 gm per kilogram, mercury has been found in the blood ten minutes after the tablet was placed in the stomach. As soon as the mercuric chlorid gets into the circulation, various pathologic changes occur rapidly. As shown by Burmeister and McNally, these changes are degenerative in character, and, if continued, lead to individual cell death. The kidney is especially affected, and these changes occur simultaneously with the presence of mercury in the circulating blood. They found that in massive intoxications the immediate renal changes will vary with the size of the dose, while in smaller doses, the renal changes will vary with the duration of the intoxication. Though the brunt of the intoxication seems to be borne by the kidney and liver, it is shown that the entire body suffers from the metal injury. Rosenbloom,² in a study of a fatal case of mercury poisoning, found mercury in practically every organ of the body, including the bones and central nervous system.

* From the Department of Medicine, University of Cincinnati College of Medicine, and the Medical Clinic, Cincinnati General Hospital

1 Burmeister, W H, and McNally, W D Mercury Poisoning, J M Res 36 87 (March) 1917

2 Rosenbloom, J A Note on the Distribution of Mercury in the Body in a Case of Acute Bichloride of Mercury Poisoning, J Biol Chem 20 123, 1915

When death occurs, it is usually the result of the kidney injury MacNider,³ who has studied the action of mercury on dogs, found that in the acute mercuric chloride intoxications death occurred, due either to the shock associated with the severe mercury enteritis, or to a delayed kidney injury, that the injury to the kidney has been constantly associated with the development of an acid intoxication, and that the delayed kidney injury is not due to the action of the mercury as such during its elimination by this organ MacNider⁴ has also demonstrated experimentally that poisoning by uranium, another heavy metal, is associated with the development of organic acids, such as diacetic acid and acetone

The kidney changes are those of an acute nephritis, there usually develops a pale, swollen kidney, perhaps with hemorrhagic areas, mostly glomerular in the more severe intoxications Menten,⁵ in a series of experiments on rabbits, found that in animals that received above 0.005 gm per kilogram, gross pathologic changes could be detected in the kidney in a short time If the dose of mercuric chloride was much smaller, for instance, 0.0012 gm per kilogram, given intravenously, microscopic changes indicating kidney injury could be detected within five minutes after the injections These changes were well defined and could be found in the liver as well as in the kidney The experimental doses of the poison were smaller when compared with the lethal dose of 0.004 gm per kilogram, as found by Barbour⁶ In one of our patients who died within nineteen hours after taking 0.03 gm per kilogram, the liver showed marked edema with but slight edema of the kidneys In another patient who died seven days after she took a similar dose necropsy revealed the most marked acute changes in the kidneys, though the liver was severely injured

In common with others,⁷ we have found certain constant changes in the blood chemical studies on animals and patients There is a retention of the nitrogenous elements, such as urea nitrogen, uric acid and creatinin, depending on the extent of the body injury, especially that of the kidney Acid intoxication, as evidenced by a reduction of the alkali reserve, is one of the most frequent findings There is also a diminution of the concentration of the whole blood chlorids With the improvement in the patient, the nitrogen elements of the blood return to normal, together with the alkali reserve and the whole blood chloride concentra-

³ MacNider, W D A Study of Acute Mercuric Chloride Intoxication in the Dog, with Special Reference to the Kidney Injury, *J Exper Med* **27** 519 (April) 1918

⁴ MacNider, W D Uranium Poisoning, *J Exper Med* **26** 1, 19 (July) 1917

⁵ Menten, M L *J M Research* **43** 315 (June-July) 1922

⁶ Barbour, H G Mercuric Chloride Poisoning in Animals Treated Unsuccessfully by Parenteral Administration of Hall's New Antidote, *J A M A* **64** 736 (Feb 27) 1915

⁷ Killian, J A *J Lab & Clin Med* **7** 129 (Dec) 1921

tion In severe intoxications, the phenolsulphonephthalein output is greatly lowered, not infrequently to zero With the improvement of the patient, the output gradually rises In several of the patients studied who had a complete anuria for a day or more and in whom the kidney functional test did not show any excretion of the dye in two hours, there was a steady rise of the phenolsulphonephthalein output with the improvement in the patient's condition In one patient the output gradually rose to 66 per cent on the thirty-third day of the disease after a complete anuria for three days and a severe oliguria for the following two There is a moderate increase in the white cell count, to as high as 20,000 or more, with an increase in polymorphonuclears A few days after the poison is taken, this increased white cell count gradually diminishes as the patient improves, or it may remain increased until death

The urinary findings are significant Albumin appears early, often several hours after the patient has taken the poison Soon there is a diminution in quantity of urine, which is often the forerunner of a complete anuria As the quantity of urine secreted diminishes, the organic elements increase, and all forms of casts and many blood and pus cells are frequently found In patients with severe intoxications, the urine is often bloody One of the most constant findings has been that the urine is highly acid to methyl red As the intoxication progresses, all signs of uremia may be present Headaches, coma and convulsions are not infrequent in this type In several of our patients, a generalized edema occurred In one patient with a total suppression of urine for three days, followed by two days when he voided only a few ounces each day, a generalized rather severe edema developed The edema of the eyelids was sufficient to obstruct his vision The entire face, neck and extremities were puffy, and a moderate amount of ascites was present This edema rapidly subsided as soon as the patient commenced to void In one of the fatal cases, in a patient who lived twenty-one days after she was poisoned, there developed marked enlargement of the submaxillary glands, herpes of the lips, pleurisy and finally terminal pneumonia

The diagnosis of mercury poisoning is not difficult The patient usually gives a clear history of taking poison The characteristic symptoms with the urinary findings are almost constant In practically all of the patients that came under observation, the vomitus, urine or feces was examined for mercury by the method of Vogel and Lee⁸ Metal has been found in the urine within fifteen hours after ingestion, but it usually does not appear in the feces before from thirty to forty

⁸ Vogel, K. M., and Lee, O. I. Detection of Mercury in the Excretions, J. A. M. A. 62: 532 (Feb 14) 1914

hours Most of it is excreted by the bowel, and can usually be detected for from seven to ten days, though in a few patients it has been found many days later

TREATMENT OF MERCURIC CHLORID POISONING

The treatment of this intoxication presents itself as a difficult problem In the last decade many so-called specifics have been presented For several of them claims are made that the mercury is placed in combination with the therapeutic agent, thereby producing a nontoxic substance which subsequently can be eliminated If the pathology of this intoxication is understood, it is evident that pathologic changes take place rapidly, depending on the severity of the irritation The problem then is how to overcome the effects of the poison The familiar cloudy swelling and later degenerative changes in the kidney are merely an example of the changes that have taken place throughout the entire body If the process continues, cell death and necrosis follow, and the organism succumbs to a generalized intoxication Knowing this, we believe that it is useless to attempt to counteract the metallic poison itself, but that our efforts should be directed toward preventing the irreparable pathologic changes that will occur if the intoxication is not combated The cloudy swelling, nephritis and uremia are associated with an increase in the production of acid bodies Fischer⁹ shows that these changes are due to the acidosis MacNider³ found this acid intoxication always associated with mercury poisoning With another heavy metal (uranium) poisoning, he found that organic acids were produced by the intoxication, and that the administration of an alkali (sodium bicarbonate) lessened the toxicity of the uranium by delaying the formation of organic acids

The logical treatment, then, seems to be to attempt to counteract any pathologic changes that have occurred, to prevent the progress of the pathologic changes, and, finally, to eliminate the toxic material as soon as possible

The treatment developed attempts to carry out that program, and, when compared with other methods of treatment, it has been fairly successful

The treatment is divided into several stages As soon as the patient comes under observation—the sooner the better—a stomach tube is introduced, and the stomach is washed with 2 quarts (liters) of a saturated solution of sodium bicarbonate This is continued until the washings return clear Before the tube is removed, 6 ounces (178 c.c.) of a saturated solution of magnesium sulphate is allowed to remain in

⁹ Fischer, M H Edema and Nephritis, New York, John Wiley & Sons, 1915

the stomach A soapsuds enema is then given Most of the patients vomit soon after taking the poison, and probably some of the mercury is eliminated in this way

To introduce alkali into the system, patients should receive an intravenous injection of alkali as soon after the preliminary treatment as possible The preparation that we have used is Fischer's solution This solution consists of crystallized sodium carbonate ($\text{Na}_2\text{CO}_3 \cdot 10 \text{ H}_2\text{O}$) 10 gm, and sodium chlorid, 15 gm, both dissolved in 1,000 cc of distilled water If this is not available, a solution of 4 per cent sodium bicarbonate may be used In patients who have not any abnormality of the circulatory system, from 1 to 15 liters can be tolerated without any difficulty In patients who have taken large amounts of poison, we have given as high as 1,800 cc at the first injection The alkaline therapy is continued by mouth We have used a modification of the old "potus imperialis" by dissolving 4 gm (1 teaspoonful) of potassium bitartrate and 2 gm ($\frac{1}{2}$ teaspoonful) of sodium citrate in a glass of water, orangeade or lemonade The patient receives 8 ounces (236 cc) of this drink from six to eight times a day, from the onset We have rarely used rectal administration of alkali in water on account of the irritation of the lower bowel associated with the bloody diarrhea Hot packs have not been used except in the few patients who had a complete suppression A liberal diet is allowed, including meat, after the diarrhea ceases

The treatment is controlled by urinalysis We endeavor to make the urine alkaline to methyl red, and keep it so Fischer has demonstrated that in patients with disease of the kidneys, the urine of whom cannot be kept alkaline to methyl red, the disease may progress and often lead to complete suppression Under this treatment the patient usually voids large quantities of urine Albumin, casts and blood are usually present for several days, and gradually diminish until the urine becomes clear Most of the patients under observation showed a normal urine from the tenth to the fourteenth day after taking the poison If the patient has taken over 7 grains (0.46 gm) of mercuric chlorid, and shows marked urinary disturbance, a second, and at times a third, intravenous injection of Fischer's solution is given The injections are given on successive days

Previously¹⁰ I have reported the results of this treatment in several groups of patients At the present time, I can report the entire series of 135 consecutive patients poisoned by some form of mercury with

10 Weiss, H B A Method of Treatment of Mercuric Chlorid Poisoning, J A M A **68** 1618 (June 2) 1917, The Treatment of Bichloride of Mercury Poisoning, Ohio State M J **13** 595 (Sept) 1917, The Principles of Treatment in Mercuric Chlorid Poisoning, with Results of Treatment, J A M A **71** 1045 (Sept 28) 1918

only eight deaths, a mortality of less than 6 per cent. These patients took from $1\frac{1}{2}$ to 50 grains (0.09 to 3.25 gm) of mercuric chlorid, usually in tablet form, or similar amounts by drinking a prepared solution or eating mercuric ointment. In only fifteen patients did a complete suppression develop. Of these, seven died, and in the other eight patients the secretion of urine was established, and the patients recovered. The patients who had the most difficulty were of the group that took over 30 grains (1.95 gm) of mercuric chlorid, and those in whom the institution of treatment was delayed.

The vast majority of the patients placed on this treatment do not develop evidence of serious kidney disease except for a moderate albuminuria, which rapidly clears. A free secretion of urine is maintained. The patient usually makes a clinical recovery in from twelve to fifteen days. Examination of several of these patients a year after they were poisoned and treated did not show any abnormality that could be connected with the poisoning.

Cincinnati General Hospital

INSULIN IN THE SEVERER FORMS OF DIABETES

WITH REPORT OF CASES *

L F FRISSELL, MD, AND JOSEPH HAJEK, MD
NEW YORK

During the winter of 1922-1923, at St Luke's Hospital, New York City, we had the opportunity to study the effect of insulin in thirty cases of diabetes, most of them severe. We report in detail thirteen in which the patients have been under long continued treatment.

Our work confirms the reports of the value of insulin in the treatment of diabetes in the publications of Drs Banting, Best and McCleod, and others of the Toronto group. Our method in general has depended on whether there has been a dangerous amount of acidosis present or not. In cases of coma or severe acidosis insulin was given immediately, and the ordinary methods of treatment, such as forced fluids by mouth or rectum with bicarbonate of soda in addition, were employed. When only a moderate amount or no acidosis was present the patients were, in the earlier cases of our series, rendered sugar free by dietary regulation before initiation of specific therapy. In the former group, immediate examinations of urine, blood sugar and the alkali reserve in the blood by the Van Slyke method were made, and usually a moderate dose of insulin, from 10 to 20 units, was given before the results of the examinations were determined. In these cases, the insulin was given at once, with orange juice or glucose, by mouth, by rectum or intravenously. When patients did not show alarming acidosis an effort was made at the start to render them sugar free on an under-nutrition diet, and later in the series they were placed on a low diet usually containing 50 gm carbohydrate, 50 gm protein and, in the absence of acidosis, 50 gm of fat. The patients were kept on this diet for a period of days until the sugar excretion was practically constant, in order to establish a preliminary period in which a patient's ability to utilize sugar without insulin administration could be determined.

Owing to the fact that the proteolytic ferments of the stomach and pancreas destroy insulin, this drug must be administered hypodermically or intravenously, and it is improbable for this reason that this mode of administration can be changed to the ordinary one by mouth. Insulin must be given with definite relationship to carbohydrate intake, as its action is dependent on having carbohydrate on which to work. Conse-

* From the Medical Service, St Luke's Hospital, New York City

quently, we have given it subcutaneously about fifteen minutes before meals with the idea that the absorption of the drug into the circulation and the carbohydrate from the digestive tract would go on at approximately the same time.

Two things are necessary first, there must be glucose in the circulation on which the insulin may act and thus prevent the development of symptoms of hypoglycemia, second, a sufficient amount of insulin should be given to take care of the carbohydrate, thus keeping the blood sugar below the threshold of excretion. Our ordinary procedure has been to determine the amount of sugar in the urine on constant diet, and to give the amount of insulin that will enable the body to utilize the same. This is no easy matter as the number of grams of carbohydrate made available by a single unit of insulin is variable, depending on the degree of function of the individual pancreas, our low figure being 0.9 gm., and our high figure 2.3 gm. The individual pancreas may vary in its insulin output so that what is true for the patient one day may not be true another day. In general, however, taking an average of 3 gm per unit and using small doses with low diet to begin with, we have been able to control glycosuria rapidly and to get the patient back on a maintenance diet.

Blood sugar determinations were made on a fasting stomach and at frequent periods after insulin administration. Contrary to the rules obtaining in the ordinary treatment of diabetes, the high figures were invariably fasting, and the low figures were those following meals and insulin administration. Consequently, when the single blood sugar was taken, we made our determinations two hours after lunch. This was done to avoid the dangers of hypoglycemia, several cases of which have been observed by those working with this new agent. The symptoms may vary from hunger, fatigue, sweating, feeling of nervousness or tremor, to convulsions and coma. The more serious symptoms we have not personally observed, although some of our afternoon blood sugar determinations have been as low as 0.05 per cent. These symptoms are speedily removed by the ingestion of carbohydrate, preferably orange juice, or in severer cases by glucose solution given by mouth, rectum or, if necessary, intravenously. All patients discharged on insulin were instructed not only in the technic of calculating and weighing their diets and the analysis of their urine for sugar, but also concerning the possibility of the advent of the symptoms characterizing hypoglycemia and the nature of these symptoms. They were also told to take orange juice if the symptoms were marked. We have not considered it advisable to discard our preconceived notions of the effect of hyperglycemia and its consequent glycosuria in reducing pancreatic

function, as shown by Allen's¹ work on experimental animals, we have, therefore, not left in the urine the "sugar pad" to protect the patient against hypoglycemia from overdosage of insulin. The problem thus resolves itself into keeping the blood sugar below the level of sugar excretion, which Williams states to be on an average 180 mg per 100 cubic centimeters although individual cases vary widely below and above this figure, and to avoid giving an insulin dosage so great as to produce symptoms of hypoglycemia. In certain instances it may be necessary to respace the insulin dosage, and even to give a small dose in the evening. Our ordinary practice, however, has been to give the largest dose before breakfast when the blood sugar is highest, and approximately equal doses before dinner and supper.

Sugar determinations in the urine have been made by the Benedict-Osterberg method by which sugar is demonstrated in normal urine in amounts varying from 1 gm or more a day. The alkali reserve is calculated by the Van Slyke method, the total blood sugar by Benedict's method and the total nitrogen by the Kjeldahl method.

The amount of glucose available to the body has been calculated in this series by adding to the carbohydrates of the diet the amount of glucose theoretically available from the protein (58 per cent). This we have calculated not from the protein of the diet, but by the urinary nitrogen as representing the total amount of protein actually metabolized in the twenty-four hour period. While more accurate than direct calculation from the diet, it is open to the disadvantage that urine collections must be exact. We have also calculated 10 per cent of the fat as available for the formation of glucose. While the work of Lusk² makes it certain that in the absolute diabetic with a dextrose nitrogen ratio of the urine of 3.65:1 such metabolism of the protein molecule does take place, it is not experimentally established that this particular utilization of the protein molecule occurs in the normal person or in the person with mild diabetes. The respiratory quotient, however, of the protein fed animal suggests that this is the case. Consequently, we feel it fair to calculate our available glucose as stated above.

CASE 1—History—A man, aged 22, single, a clerk, born in the United States, had had diabetes since September, 1922. He was admitted to the hospital on Dec 11, 1922, he was discharged on March 3, 1923. (He was then followed in the diabetic clinic.) In September, 1922, he had an alveolar abscess which ruptured and continued to discharge for two weeks, at the end of which time the tooth was finally extracted. At about the same time he noticed weakness, lassitude and loss of weight. Examination of the urine revealed sugar in large amount—149 gm. The patient had had malaria in 1918. His family history was negative.

¹ Allen, F. M. Glycosuria and Diabetes, Cambridge, Harvard University Press, 1913.

² Lusk, G. Elements of the Science of Nutrition, Philadelphia, W. B. Saunders Company, 1919.

Physical Examination—Examination revealed marked undernutrition, it was otherwise negative. The patient weighed 102 pounds (46.26 kg). Sugar utilization. In the preliminary period after the administration of sugar the plus balance was 6.

During February the utilization per insulin unit was 16, last week observed utilization per insulin unit was 23.3.

Treatment and Course—On the first day of admission to the hospital he was put on a diet of carbohydrate, 50 gm, protein, 25 gm, fat, 20 gm, and on this diet excreted 149 gm of sugar. For the next week an effort was successfully made to render him sugar free by undernutrition with four starvation days, yet during the first four days he showed sugar in his urine derived entirely from body protein, if we except the possibility that the excretion of the first day or two represents glucose previously ingested. On the ninth day, he was given 9 units of insulin and a diet of carbohydrate, 50 gm, protein, 50 gm, fat, 50 gm. He remained sugar free from that time on a diet gradually increased to from 600 to 3,000 calories with 200 gm of available glucose on the same insulin dosage. The blood sugar remained between 95 and 125 mg. Fatigue and lassitude disappeared when a maintenance diet was attained. His weight increased from 100 to 122 pounds (45.35 to 55.33 kg), and for the past two months he has resumed his work, weighing his food, analyzing his urine and administering insulin to himself.

Comment—We have here the problem of an absolute diabetic, certainly so when first observed, his diet for the first day furnishing a possible 64 gm of sugar, while the excretion was 149 gm, the excess of nitrogen of urine over nitrogen of food being 67 gm. We can thus assign 64 gm of sugar to his diet, 25 gm as derived from destruction of body protein (a loss of 41.8 gm), while the remaining 60 gm represent carbohydrate previously ingested. Not until the fifth day did the dextrose nitrogen ratio of the urine reach 2:1, the urinary sugar still being derived in part from body protein. Yet this patient five months later was able to utilize 220 gm of sugar on 9 units of insulin or, if we calculate in the ordinary way, of sugar utilizable before and after insulin, 23.3 gm per unit. Does this figure represent the truth, or has a restoration of pancreatic function taken place? The latter seems far more probable than that the insulin unit has been able to cause directly the burning of such increasing amounts of carbohydrate. In no other case in the series has the pancreatic function thus increased. The history too is significant, as symptomatic diabetes followed a tooth infection of severe nature, and it is probable that the pancreatic function if previously impaired was much damaged by the infection.

A complete laboratory report of this case, during the patient's stay in the hospital, is given below, in addition to the graphic charts (Figs 1, 2, 3 and 4).

CASE 2—History—A man, aged 20, single, a chauffeur, born in the United States, had had diabetes for one and one half years. He was admitted to the hospital on March 22, 1923. He said he thought diabetes followed an automobile accident. On January 23 he consulted a physician because he was

Laboratory Report in Case 1

D'te	Urine, 24 Hrs, O°c	Ht Wt	Food				Urine				Blood				Miscellaneous				Units Insu- lin
			Carbohydrate, Gm	Protein, Gm	Fat, Gm	Total Chlorides	Specific Gravity	Rene- tion	Albu- min	Ferri- Chloride	Nitro- plus std	Sug'r per Cent	Tot'l Sug'r Gm	Nitro- gen of Food	Carbon Dioxi- d, % by Volume	Sugar Mg	Glucose Avail- able	Glucose Util- ized	
2/18/22	2,400	100	100	100	70	1,700	1.030	Acid	v ft	++	2	4.80	12.0	8.0	101.6	-47.4			
2/19/22	2,650	102	50	50	25	2,650	1.019	Acid	v ft	++	5.62	149.0	10.7	4.0	91.54	-57.46			
2/20/22	2,650	102	50	25	5	2,650	1.014	Acid	v ft	++	5.62	149.0	12.2	4.0	60.59	-9.91			
2/21/22	2,650	102	50	25	5	2,650	1.012	Acid	v ft	++	3	79.5	52.8						
2/22/22	2,550	100	0	0	0	2,550	1.008	Acid	v ft	++	2	51.0	8.92	0	32.56	-18.44			
2/23/22	2,24/22	100	0	0	0	2/23/22	1.010	Acid	v ft	++	0.0372	8.9	4.4	0	16.06	+7.16			
2/24/22	2,400	100	0	0	0	2/24/22	1.005	Acid	v ft	++									
Week																			
2/25/22	2,200	102	25	25	0	2,25/22	200	1.007	Acid	v ft	++	0.0357	7.85	7.5	4.0	52.37	44.52		
2/26/22	1,800	102	25	25	0	2/26/22	200	1.005	Acid	v ft	++	0.0357	6.75	10.3	4.0	62.59	55.84		
2/27/22	1,750	102	25	25	0	2/27/22	200	1.007	Acid	v ft	++	0.0357	8.75	6.65	1.0	48.72	39.97		
2/28/22	2,500	105	0	0	35	2/28/22	1.003	Acid	v ft	++	0	1.12	6.3	0	22.99	21.87			
2/29/22	1,700	105½	35	35	35	2/29/22	1.005	Acid	v ft	++	0	1.28	6.1	6.8	53.76	57.48	0		
2/30/22	1,900	108½	35	35	35	2/30/22	505	Acid	v ft	++	0	1.28	5.8						
2/31/22	2,900	110	50	50	50	2/31/22	950	1.006	Acid	v ft	+	0	0.035	2.16	9.8	8	90.77	88.31	9
Week																		27	
3/1/22	3,150	108	50	50	50	3/1/22	950	1.005	Alk-Line	v ft	+	0	0.034	1.07	105.1 m	7.7	4.5		
3/2/22	2,360	108	50	50	50	3/2/22	950	1.003	Acid	v ft	0	0	0.038	1.6	105 p m	8.8	8		
3/3/22	2,200	110	50	50	60	3/3/22	1,040	1.007	Acid	v ft	0	0	0.036	1.23	125 p m	5.95	8		
3/4/22	3,100	110	50	50	70	3/4/22	1,026	1.003	Acid	v ft	0	0	0.031	0.96	125 p m	8.45	8		
3/5/22	3,250	110	50	60	80	3/5/22	1,254	1.003	Acid	v ft	+	0	0.075	2.43	95 p m	8.2	9.6		
3/6/22	50	60	80	80	1,160	3/6/22	1,015	Acid	v ft	0	0	0	0.062	0	71 p m	100 p m			
3/7/22	3,150	50	60	80	1,160	3/7/22	1,005	Acid	v ft	0	+	1.95	0.95	0.1	9.1	9.7			
Week																		27	
3/8/22	2,600	108	70	90	100	3/8/22	1,290	1.007	v ft	0	0	0	0.050	1.3	105 p m	8.2	10		
3/9/22	2,320	108	70	90	100	3/9/22	1,453	1.008	v ft	0	0	0	0.027	0.63	105 p m	8.2	12.2		
3/10/22	2,400	107	60	100	100	3/10/22	1,449	1.007	v ft	0	0	0	0.027	0.91	100 p m	11.3	12.4		
3/11/22	3,650	105½	60	60	100	3/11/22	1,446	1.006	v ft	0	0	0	0.022	0.81	95 a m	10.1	12.08		
3/12/22	3,750	104	60	75	130	3/12/22	1,710	1.007	v ft	0	0	0	0.026	0.925	87 p m	12.6	12		
3/13/22	1,12/22	103	60	75	130	3/13/22	1,710	1.010	v ft	0	+	0	0.024	0.48	125 p m	7.1	12		
Week																		27	
3/14/22	2,000	103	60	75	130	3/14/22	1,009	v ft	0	0	+	0	0.035	0.95	v ft	11.7			
3/15/22	2,600	103	60	75	130	3/15/22	1,710	1.008	v ft	0	0	0	0.023	0.53	v ft	10.5	12		
3/16/22	2,300	105	65	85	140	3/16/22	1,860	1.012	v ft	0	0	0	0.025	0.75	v ft	7.4	12		
3/17/22	2,500	105	65	85	140	3/17/22	1,860	1.006	v ft	0	0	0	0.021	0.86	v ft	9.05	13.6		
3/18/22	3,600	105	65	85	140	3/18/22	1,860	1.008	v ft	0	0	0	0.021	0.52	v ft	11.4	13.6		
3/19/22	2,500	104	65	85	140	3/19/22	1,860	1.008	v ft	0	0	0	0.021	0.52	v ft	11.6	13.6		

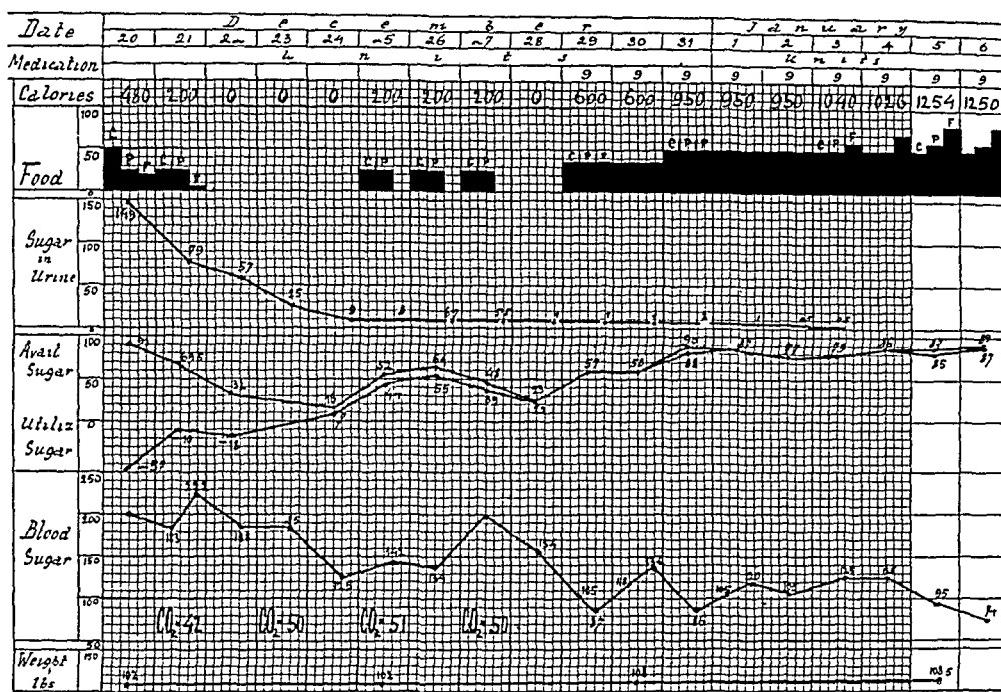


Fig 1 (Case 1) —Daily graphic of insulin administration, food intake, sugar excretion in urine and amount of glucose utilized, also blood sugar curve, carbon dioxide in blood and the weight of the patient from Dec 20, 1922, to Jan 6, 1923, weight December 20, 102 pounds (46.26 kg.)

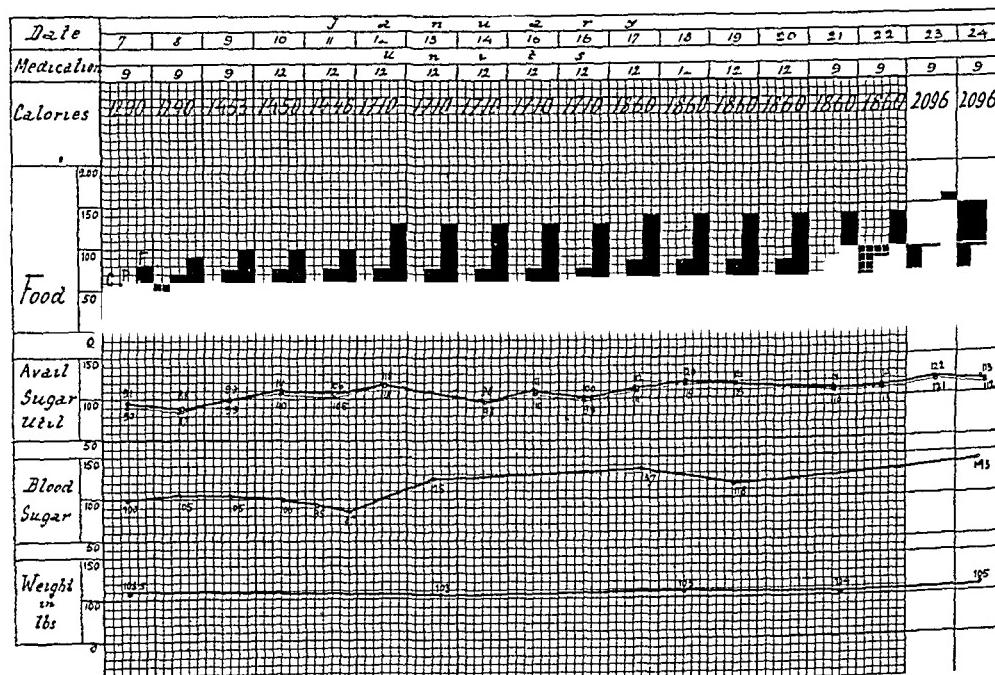


Fig 2 (Case 1) —Same data as in Chart 1, for period January 7 to 24

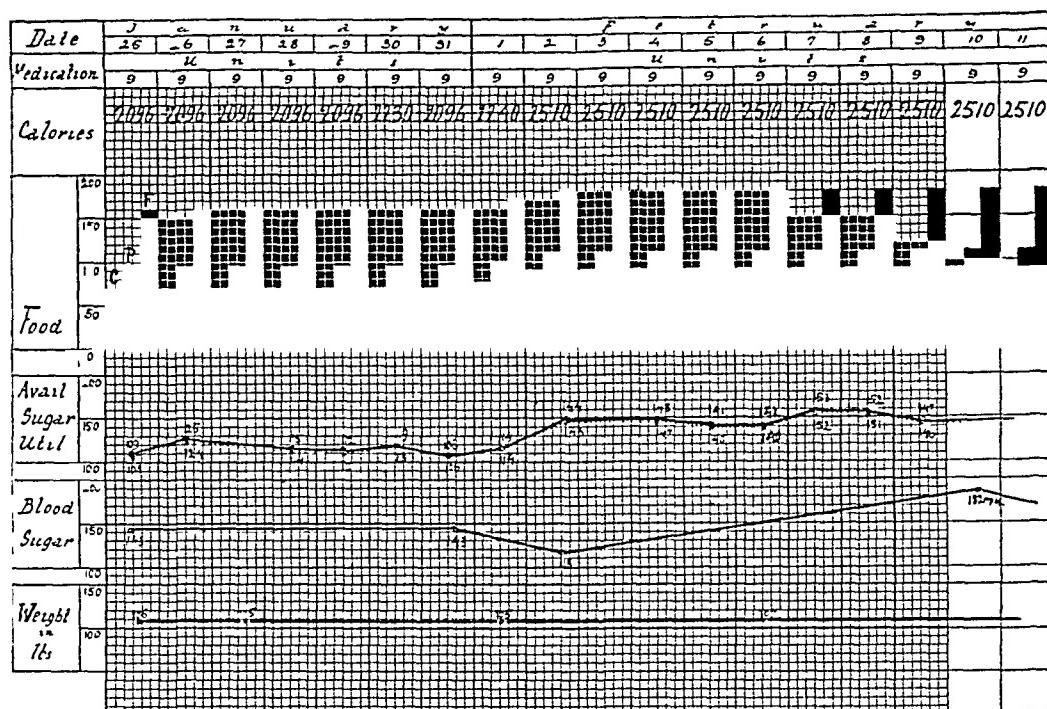


Fig 3 (Case 1) —Period from January 25 to February 11

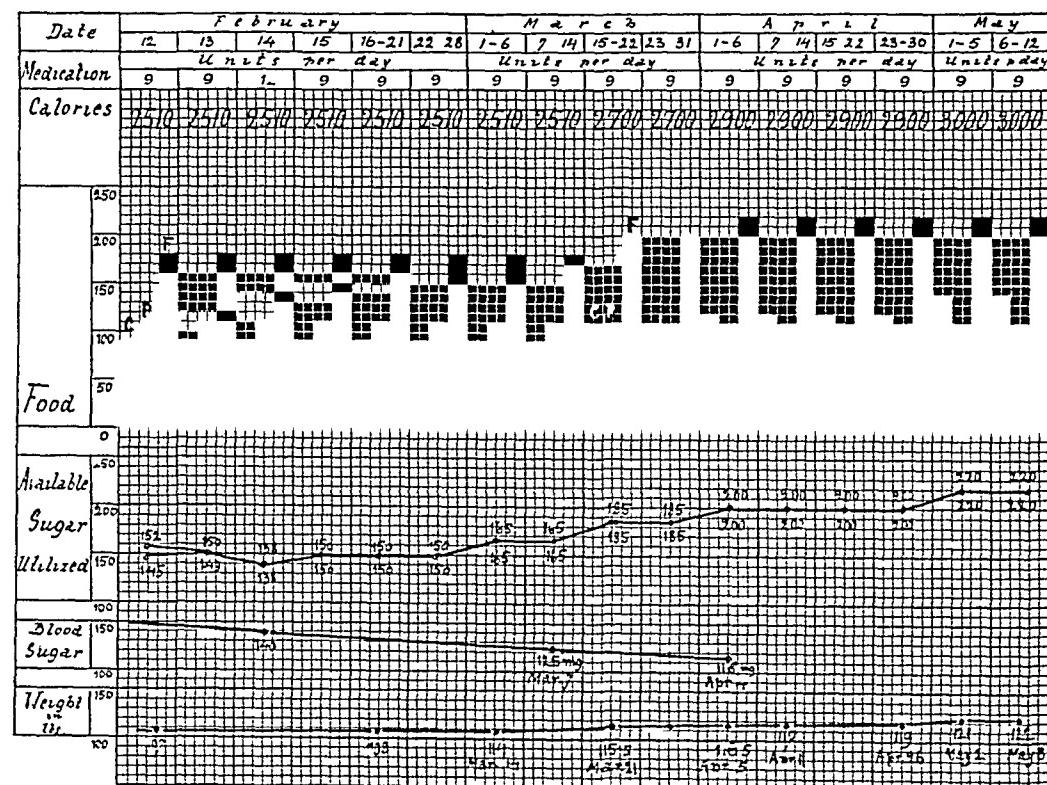


Fig 4 (Case 1) —Period from February 12 to May 12, weight, May 12, 122 pounds (55.33 kg.)

losing weight rapidly A diagnosis of diabetes was made The patient had had measles, scarlet fever and pneumonia in childhood His family history was negative

Physical Examination—This revealed nothing of importance, except two bad teeth, which were removed On admission to the hospital he weighed 98 pounds (42.45 kg), on May 1, 1923, 112 pounds (50.8 kg) Sugar in the urine was 20 gm, blood sugar, 300 mg

Treatment and Course—As the patient was much emaciated, he was put on insulin immediately, and the diet was rapidly increased to a maintenance value of 2,000 calories, the insulin dosage was increased simultaneously from 15 to 45 units The patient was an unintelligent person who constantly stole food in spite of gain in weight and a sufficient diet, so that we regard the outcome of his case when discharged from the hospital as problematical Tooth infection was present in this case also

CASE 3—History—A man, aged 31, married, a clerk, born in Russia, had had diabetes for one year He was admitted to the hospital on Jan 8, 1923, and discharged on March 22, 1923 The patient had the usual symptoms of diabetes He had had an appendectomy performed in 1921 There were no other infections The family history could not be obtained His parents were in Russia

Physical Examination—The examination was negative The patient's weight on admission was 94 pounds (40.63 kg), weight on discharge, 101½ pounds (46.03 kg) The sugar content of the urine was 70 gm, the blood sugar, 65 mg

Treatment and Course—The patient was put on a low diet, and on account of acidosis fat was excluded He was starved on the sixth and seventh days, becoming practically sugar free Twelve units of insulin were given on the ninth day on a diet of carbohydrate, 25 gm, protein, 50 gm, fat, 50 gm On 12, and later 9 units of insulin, the diet was increased to 1,560 calories, and finally to 2,250 calories, with an insulin dosage of 18 units, rendering him not quite sugar free The case was complicated by a tendency to steal The weight increased gradually As he was a person of low intelligence, an effort was made after two months of treatment to put him on a diet of 1,300 calories without insulin Sugar, however, reappeared on this diet, and on his own insistence he was sent home on insulin, but he has not reported to the follow-up clinic His case is of importance as illustrating the difficulty of treating a diabetic patient who will not cooperate, and whose grade of intelligence is low

CASE 4—History—A man, aged 47, married, a policeman, born in Ireland, had had diabetes since September, 1922 He was admitted to the hospital on Nov 20, 1922, he was discharged on Jan 26, 1923 He had had no infectious diseases He took whisky every day His family history was negative

Physical Examination—This revealed nothing of importance but an enlarged liver

Treatment and Course—He was given insulin from Dec 18, 1922, to Jan 18, 1923, receiving 9 units the first two days, 12 units the next twelve days, 15 units for the next six days and 18 units for the remaining 9 days His weight on admission was 170 pounds (77.11 kg), weight on discharge, 166 pounds (75.29 kg) He was sugar free on 1,520 calories and 50 gm of carbohydrate While on insulin, the patient was receiving a diet consisting of 70 gm of carbohydrate, 100 gm of protein and 190 gm of fat On January 18, insulin was stopped, and the diet changed to 50 gm of carbohydrate, 60 gm of protein and 140 gm of fat, on which he remained sugar free He is being followed in the diabetic clinic and is sugar free at the present time on more or less the same diet

Comment—The patient in the foregoing case is of interest because he shows slight increase in pancreatic function after a month's treatment

with rather small doses of insulin. On a diet of 1,610 calories he was able to utilize 92 gm of glucose, on the same diet in the after period he utilized 104 gm, a gain of 12 gm a day. Sugar utilization during the preliminary period was 91 gm, last week observed, 123 gm, after period, 104 gm, per insulin unit, 17 gm.

CASE 5—History—A woman, aged 33, married, a clerk, born in the United States, had had diabetes for six years. From 1911 until 1918 she was subject to frequent attacks of quinsy sore throat. She remembered having quinsy on Thanksgiving day, 1917, and again in February, 1918. In March she was said to have had diabetic coma. She was told by a physician, in 1917, that she had diabetes. In June, 1918, her tonsils were removed, since then she had felt much better. She had had measles, scarlet fever and whooping cough when a child. She had been married for fifteen years. She had two children, aged 9 and 12, respectively. She had had a therapeutic abortion because of diabetes in May, 1918, no miscarriages. Her father died of diabetes at the age of 45. Otherwise the family history was negative.

First Admission—She was admitted on Aug 2, 1922, and discharged on Aug 19, 1922. She showed 3 per cent of sugar in the urine and 200 mg of blood sugar and a faint trace of diacetic acid and acetone. Her weight on admission was 120 pounds, weight Aug 12, 1922, 117½ pounds (53.29 kg). The patient became sugar free in three days on a diet consisting of 50 gm of protein, 50 gm of carbohydrate, and 50 gm of fat, with one starvation day. She was discharged on August 18, receiving 100 gm of carbohydrate, 100 gm of protein and 120 gm of fat, showing a faint trace of sugar in the urine. In the diabetes clinic, where she was under observation up to her second admission, examination revealed sugar at intervals.

Second Admission—The patient was readmitted on Dec 11, 1922, and put on insulin medication on Dec 19, 1922.

Physical Examination—The examination was negative. The patient's weight on Dec 15, 1922, was 115½ pounds (52.38 kg), her weight on May 1, 1923, was 124 pounds (56.24 kg).

Treatment and Course—On her readmission she was rendered sugar free by undernutrition. The diet was not a maintenance one, showing a tolerance of 66 gm of sugar on a diet of 1,000 calories. The blood sugar, however, varied from 170 to 214, a high threshold. The patient was, therefore, put on a small dosage of insulin, 3 units a day, which was increased with the increase in her diet to 12 units when on the twenty-fourth day she showed slight symptoms of insulin shock with a blood sugar content of 76 on a diet of 1,350 calories. The symptoms consisted of nervousness, tremor and sweating which disappeared rapidly after the administration of a glass of orange juice. During the subsequent two days she was kept on a 9 unit dosage, the blood sugar rising to 182 mg in the morning and 166 mg in the afternoon, when she was again given 12 units of insulin without having any symptoms. As she continued to lose weight on this diet, the number of calories in her diet was increased, first to 1,860, then to 2,295 on February 3, with an insulin dosage of 18 and finally 29 units. The course of her disease has been interrupted by several diarrheal attacks, and at present she is on a diet containing 120 gm of available glucose. Her carbohydrate utilization per insulin unit has varied with different lots of insulin—3.5, 2.4, 1.6, 3.5, 3.2, 3.2, 2.9 and 3 gm.

Comment—The patient had a moderately severe diabetes, but could not maintain herself sugar free on a maintenance diet. On a somewhat large dosage of insulin she is now maintaining herself, and instead of

being in her previous condition of emaciation is approximately of normal weight. She is able to do her work without fatigue, and has thus regained her economic status.

CASE 6—History—A woman, aged 50, a widow, a housewife, born in Austria, had had diabetes for seven years. She was admitted to the hospital Jan 2, 1923, and discharged on March 8, 1923. She complained of inability to walk because of severe pain in her left knee. She had had measles, diphtheria, whooping cough and frequent attacks of cold and sore throat, especially during the last seven years. She had been married for twenty-five years. She had never been pregnant. Menopause occurred at the age of 47. Her father had died of diabetes at the age of 60. Her mother was living and well. Two sisters and one brother were well. One sister had diabetes. Her husband died of blood poisoning.

Physical Examination—The patient had large, infected tonsils (operation refused) and evidences of osteo-arthritis in both knees. There was also a low grade infection of the sinuses. Her weight on admission was 125 pounds (56.69 kg.), on discharge it was 129 pounds (58.31 kg.). Sugar content of the urine was 50 mg., blood sugar, 250 mg.

Treatment and Course—In the hospital she was kept on a low diet for ten days with one day of actual starvation, with the result that at the end of that time on a diet of 260 calories with 43 gm of available sugar she was excreting 12 gm of sugar in the urine with a blood sugar content of 232 mg. She was then given insulin—at first 9 units and later 12 units, the diet was gradually increased to 2,000 units with 138 gm of available sugar, she was then sugar free with a blood sugar of 130 mg.

Comment—This patient also presents the clinical picture of a severe diabetes, manufacturing sugar from her body protein on a low diet. Her condition was easily controlled by small doses of insulin. The sugar utilization of her preliminary period was 32 gm, during February, 5 gm of carbohydrate utilization per insulin unit, and on discharge 77 gm per insulin unit, showing in all probability an increase in pancreatic function.

CASE 7—History—A school girl, aged 8, born in the United States, was admitted to the hospital on Jan 25, 1923, and discharged on April 18, 1923. Three months prior to admission the three youngest of the six children in the family became jaundiced. (In the same school there were also fourteen other cases of jaundice.) The jaundice lasted for about one month, when the three children developed a ravenous appetite and drank large quantities of water. All three began to lose weight rapidly, in spite of the fact that they were consuming large amounts of food. Two weeks after the jaundice cleared up the three children came down with scarlet fever. Examination of the urine made at that time revealed 2 per cent of sugar for the other two children, while Rose had 5 per cent with a polydipsia and polyphagia. Apparently this dated from the onset of the jaundice. This child had had measles at the age of 3 weeks, chickenpox and whooping cough at the age of 3, German measles when 4 years old and mumps at the age of 6. All three children were admitted to St. Luke's Hospital. The other two had a mild form of diabetes, and are now sugar-free on a moderately restricted diet.

Physical Examination—Physical examination of Rose was negative. Her weight on admission was 35 pounds (15.87 kg.), on discharge it was 42 $\frac{1}{4}$ pounds (19.39 kg.). The sugar content of the urine was 42 mg., the blood sugar, 82 mg. Sugar utilization during the preliminary period was 64 gm. Sugar utilization

tion during last week observed was 133 gm. Sugar utilization per insulin unit was 8 gm. On admission she was passing 42 gm of sugar on a diet giving her 51 gm of available sugar. The blood sugar was 182 mg., carbon dioxide content, 44.

Treatment and Course.—On the third day she was given 4 units of insulin to control acidosis, and on the thirtieth day her blood sugar was 120 mg., the carbon dioxide content was 52 mg. The diet was rapidly increased to a maintenance diet of 2,020 calories containing 145 gm of available sugar. At this time she was receiving 8 units of insulin a day. Her total gain in weight was 10 pounds (4.5 kg.), and instead of being an emaciated, unhappy child she is now a normal little girl. At the time of discharge she had a little sugar in the urine, probably due to stealing—a trick she had learned from two little boys in the ward.

Comment.—The interesting fact about the family in Case 7 is the development in three of its members of diabetes following infectious jaundice, of whom a girl aged 8 had the only severe case. The blood sugar curves after glucose ingestion of the other two, however, were typically diabetic, although they were readily kept sugar free by moderate restriction of diet, simply eliminating sugar and sweets. We wish to emphasize the fact of the importance of acute infections in relationship to the onset of diabetes.

CASE 8—History.—A school boy, aged 7, born in the United States, had had diabetes for three years. He had had two previous admissions, and was discharged, sugar free, on a fairly good tolerance of carbohydrate, 60 gm., fat 60 gm., and protein, 90 gm., but at home he would not live on his diet, and he was readmitted on Sept 9, 1922. After an unsuccessful effort to render him sugar free by undernutrition, he was put on a diet of approximately 1,000 calories, showing sugar continuously, and with a blood sugar of 182 mg. He had been reduced to a skeleton, weighing 40 pounds (18.14 kg.). His father was living and well, his mother died of pneumonia, his aunt had diabetes.

Physical Examination.—The examination was negative except for extreme undernutrition.

Treatment and Course.—When insulin became available, he was kept on a 1,000 calorie diet, and on this showed glucose utilization of 61 gm., although he was passing at the time from 40 to 60 gm of sugar in his urine. He had been an inveterate stealer of food, and for that reason was kept for the first six weeks of the insulin experiment in a room by himself under lock and key. On an insulin administration of 9 units he was rendered sugar free, on a diet containing 1,500 calories and 123 gm of available sugar, his blood sugar falling from 182 to 125 mg., and at times in the afternoon as low as 55 mg without symptoms of hypoglycemia. The diet was gradually increased, until at the end of April he was receiving 2,100 calories on 27 units of insulin a day, showing, however, at times 5 gm of sugar. His weight, which had been low, continued so until nitrogen equilibrium was established, at which time he was getting a diet of approximately 1,600 calories, from which time on it rapidly increased until on his discharge he weighed 64½ pounds (29.25 kg.). His stealing propensity, however, made the case difficult. On one occasion he even forged his diet orders. It is therefore not surprising to find that at the mid-period, when not perfectly controlled, his utilization per insulin unit varied. He took care at one time of 7 gm of glucose per unit in the period from February 13 to February 20, 3 gm., and in the period from April 25 to 30, 4 gm per unit. He is now at home on insulin treatment perfectly trained in the simple analysis of his urine and in the calculation of his diet.

Comment—Treatment of this patient will probably not be successful, as in spite of an overliberal diet on which it seemed wise to put him he will probably take additional food. Although he had severe diabetes and his pancreatic function had been much impaired by dietary excess, he was perfectly amenable to treatment. Incidentally, this is the



Figure 5

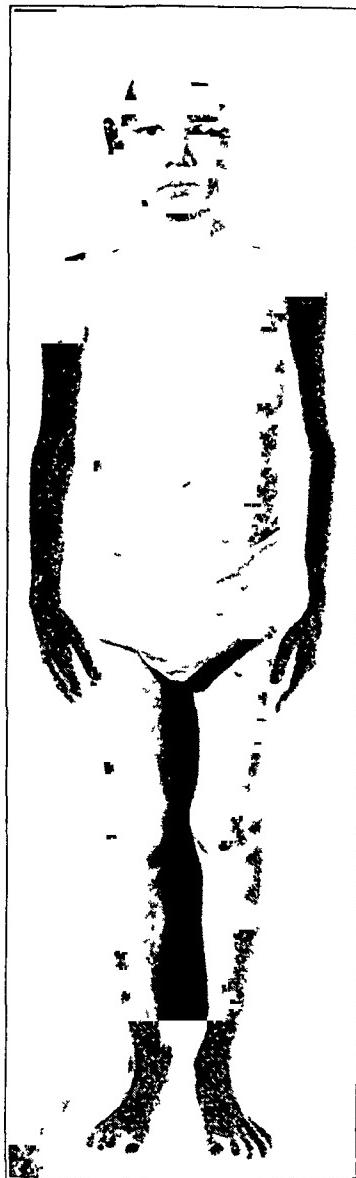


Figure 6



Figure 7

Fig 5 (Case 8)—Taken Dec 20, 1922, before administration of insulin. Weight, 40 pounds (18.1 kg). Note extreme undernutrition and facial expression.

Fig 6 (Case 8)—Jan 29, 1923, weight, 48½ pounds (21.9 kg).

Fig 7 (Case 8)—March 10, 1923, weight, 55 pounds (24.9 kg). Weight May 1, 1923, was 64½ pounds (29.2 kg).

one patient in our series who showed an anaphylactic reaction consisting of marked urticaria. In this case one of the earlier preparations of insulin was used. The condition was rapidly controlled by desensitization with fractional doses, after which insulin was again administered.

CASE 9—History.—A woman, aged 53, single, a housewife, born in France had had diabetes since 1913. She was admitted on March 3, 1923, in coma, with signs of lobar pneumonia. She was discharged on April 25, 1923. She had been subject to attacks of asthma since she was 20 years old. Her last attack occurred in 1920. Since then she had been free from attacks. She had diphtheria when she was 20 years old. Her tonsils had been removed at the age of 21. She had had a carbuncle in 1922. Her mother's aunt had diabetes.

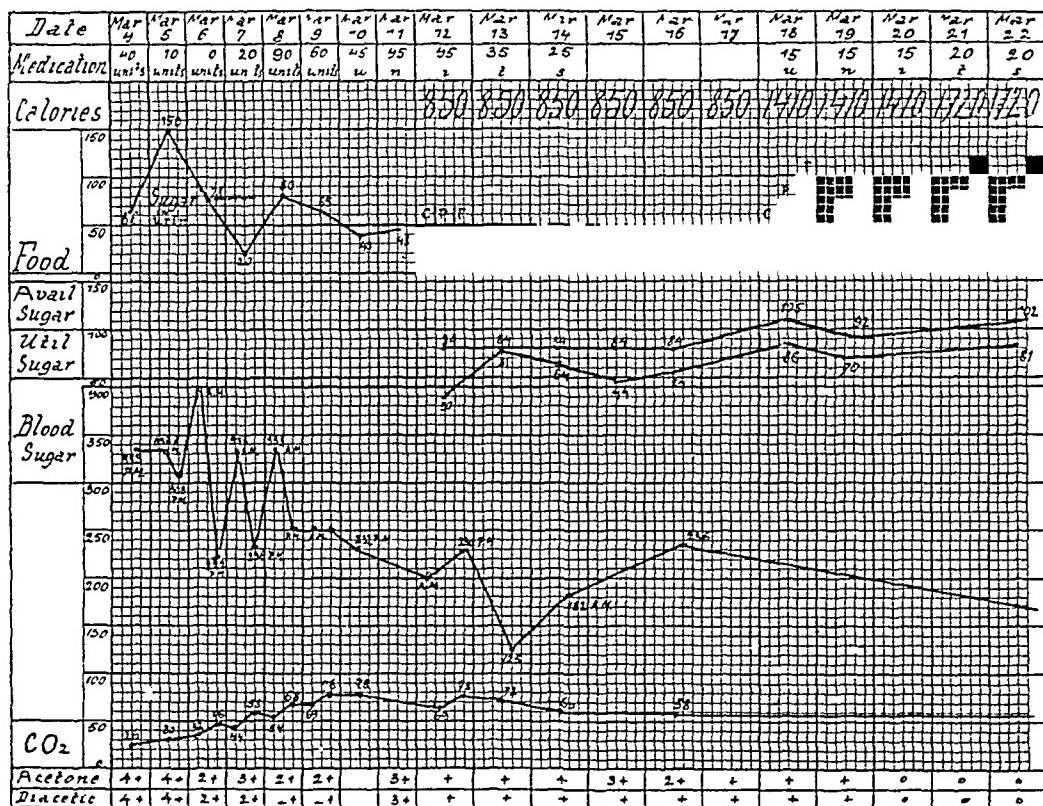


Fig 8 (Case 9)—Patient in coma on admission, showing 66 gm of sugar in urine, 333 mg in blood, carbon dioxide 26 per cent by volume, acetone and diacetic acid 4+ with physical signs of lobar pneumonia. At the end of ten days, during which she received 700 units of insulin as shown above she was able to utilize 80 gm of glucose, the blood sugar fell to 125 mg, the carbon dioxide rose to 72 per cent by volume, acetone and diacetic acid were 1+. On March 20, the patient was free from acidosis.

Her grandfather had died in an attack of asthma. On March 26, 1923, she weighed 117 pounds (53.07 kg), on May 12, 1923, 126 pounds (57.15 kg).

Physical Examination.—Examination revealed pneumonia of the right middle and lower lobes. Sugar utilization during the preliminary period was 35 gm, sugar utilization during last week observed, 105 gm, sugar utilization per insulin unit, 14 gm.

Treatment and Course.—She was admitted to the hospital in coma with a Group IV pneumonia, a blood sugar content of 333 mg, and a carbon dioxide

content of 26. Forty units of insulin were given at once. On a dosage of 110 units of insulin daily the acidosis was controlled within forty-eight hours, the pneumonia running its usual course with defervescence on the eighth day. During the acute illness the diet at first consisted of gruel and orange juice, later milk was added, and on March 12, the patient was put on a solid diet of carbohydrate, 50 gm, protein, 50 gm, fat, 50 gm, this was subsequently increased to 2,200 calories with 165 gm of available sugar. May 12, she had been sugar free for a month, with a blood sugar of 111.

Comment—The case is one of those almost invariably fatal when treated by the old method—a coma complicating a severe acute infection—and shows that with insulin the coma may be relieved when the infection runs its ordinary course.

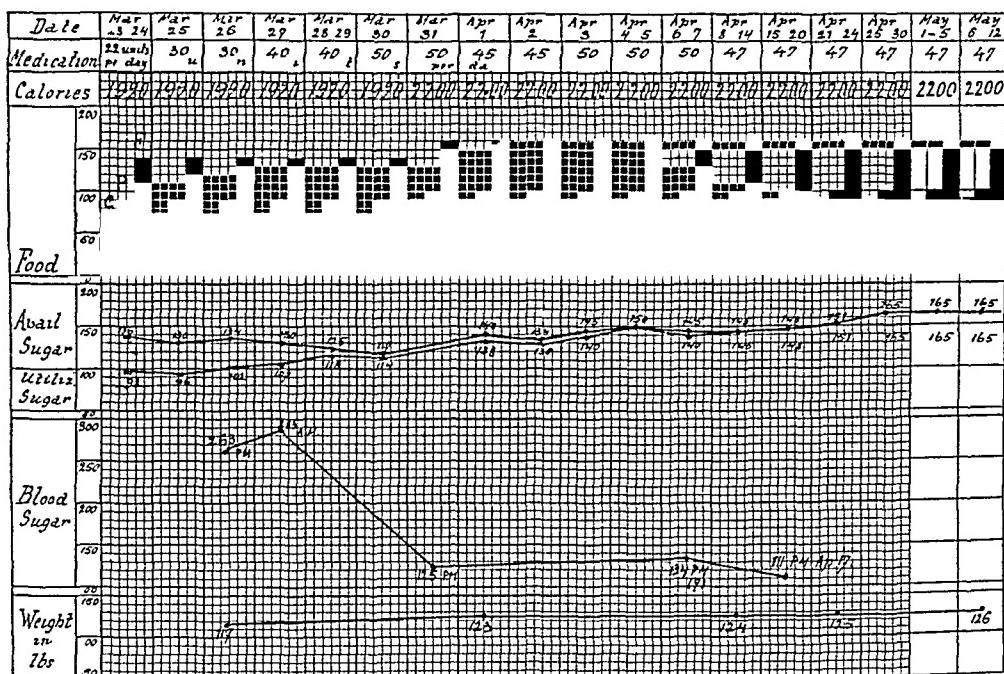


Fig 9 (Case 9)—The progress of the patient from March 23 to May 12, giving daily dose of insulin and the diet, showing also the amount of glucose utilized, the blood sugar curve and the weight.

CASE 10—History—A school boy, aged 8, born in the United States, had had diabetes for one year. He was admitted to the hospital on April 13, 1921, and discharged on June 30, 1922. A month prior to admission he had had an attack of German measles which had lasted several days. After recovery his mother noticed excessive thirst, hunger and polyuria, with gradual loss of weight and drowsiness. He was taken to a physician, who made a diagnosis of diabetes. The family history was negative. Past history was negative, except for German measles.

Treatment—The patient was discharged from the hospital sugar-free on a diet consisting of 120 gm of fat, 70 gm of protein and 150 gm of carbohydrate. He was followed up in the pediatric clinic and on December 22, the Klebs-Löffler bacillus was found in his throat. He was sent to a municipal hospital, where his diet was neglected. The diabetes became much worse, and acetone appeared in the urine again in January, 1923. He was readmitted to the hospital

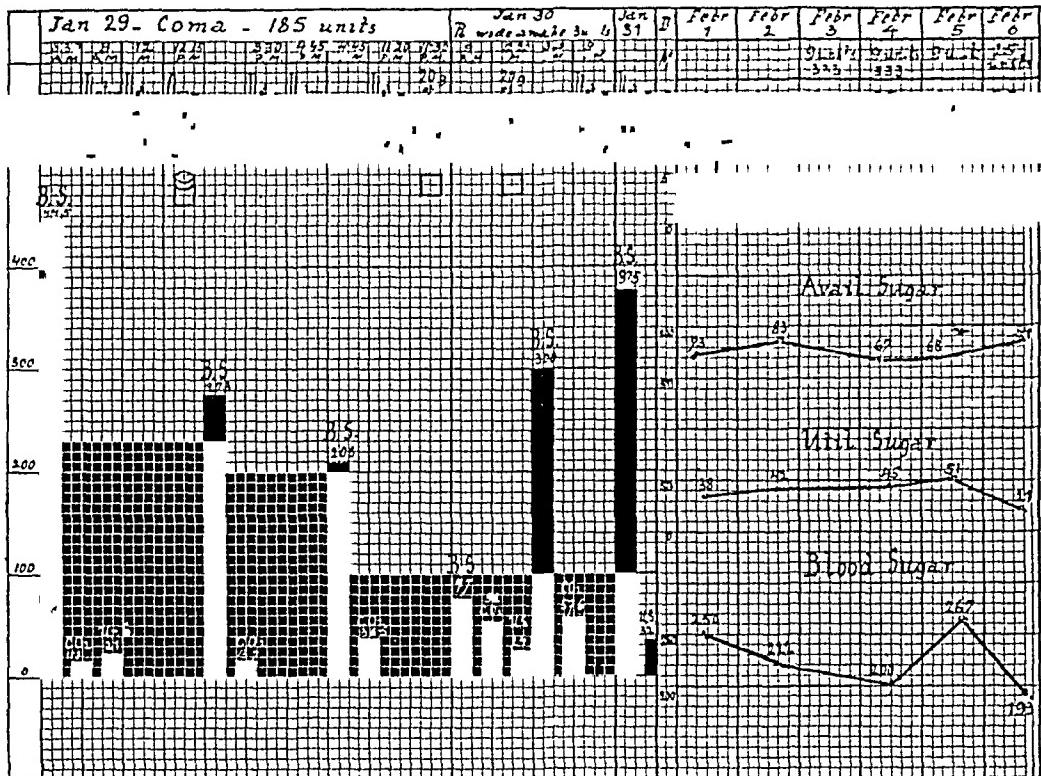


Fig 10 (Case 10).—Patient admitted in coma at 8:30 a.m., on Jan 29, 1923. Observe rapid fall of blood sugar from 445 mg to 77 mg and rise of carbon dioxide from 118 to 52 per cent by volume following administration of 185 units within twenty-four hours when he came out of the coma.

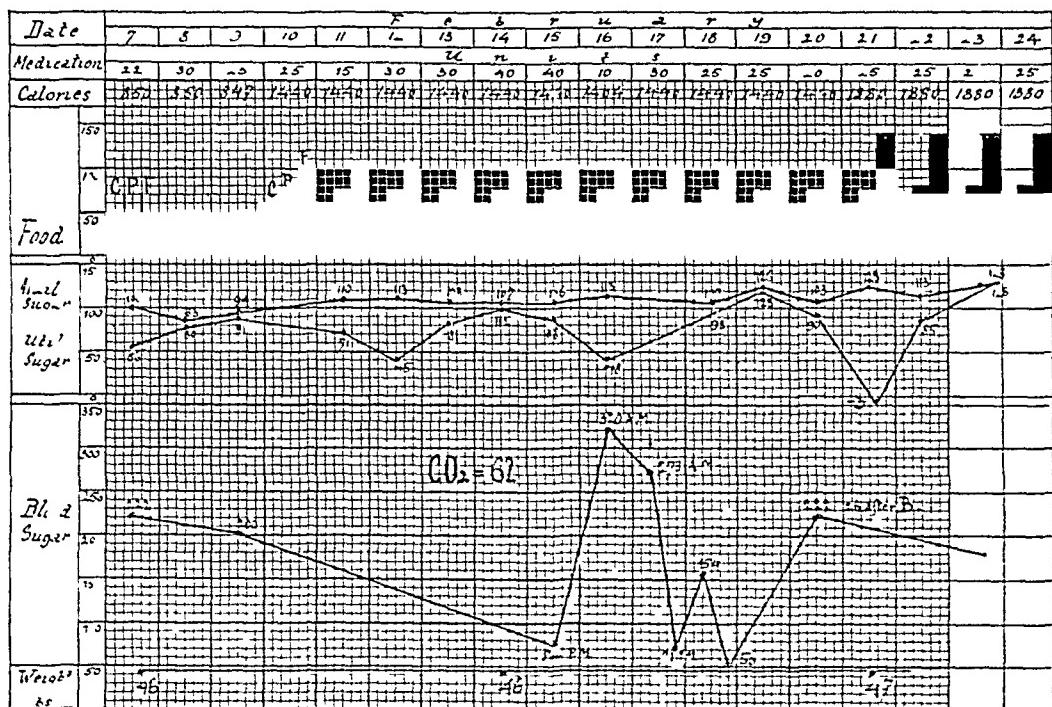


Fig 11 (Case 10) — Progress of the patient from February 7 to February 24
Note marked increase in diet

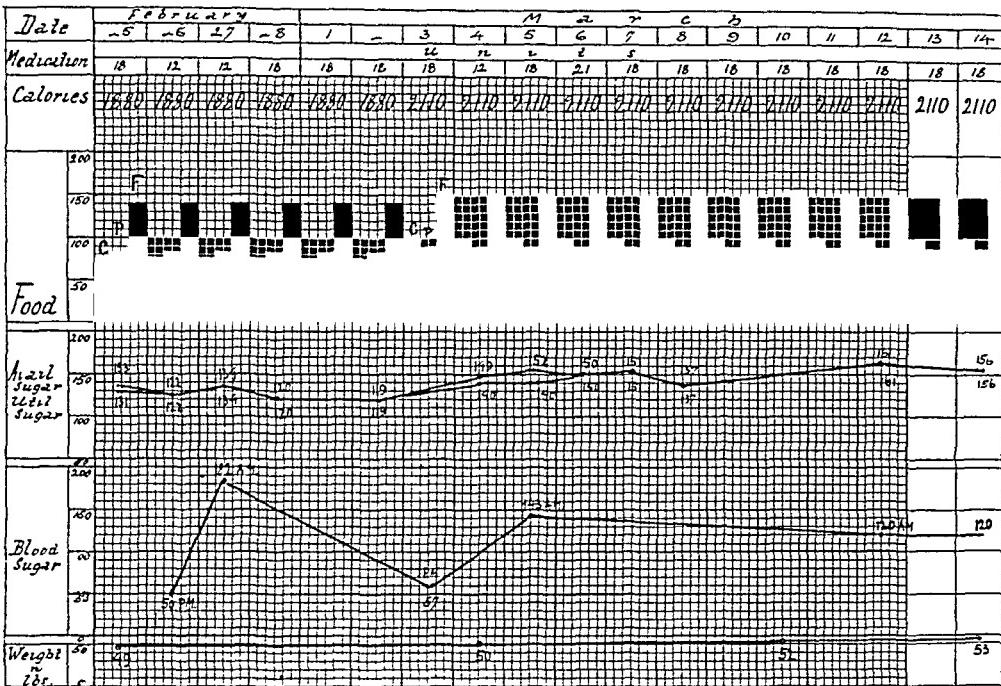


Fig 12 (Case 10)—Period from February 25 to March 14.

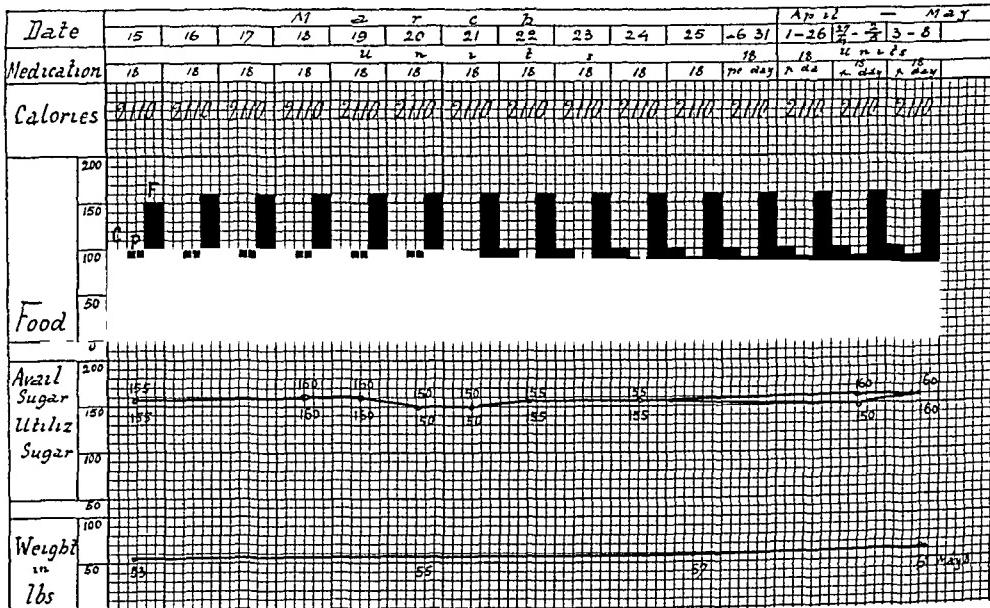


Fig 13 (Case 10) — Period from March 15 to May 8. The patient was now utilizing 155 gm of glucose, daily dose of insulin, 18 units, increase in weight since February 7, 15 pounds (6.8 kg).

for the second time in coma. His weight on admission was 46 pounds (20.86 kg.), the carbon dioxide content of the blood was 11.8. His weight on discharge, May 8, 1923, was 61 pounds (27.66 kg.) the carbon dioxide content of the blood was normal. He was then put on a diet consisting of 90 gm of protein, 150 gm of fat and 120 gm of carbohydrate. The sugar utilization during the preliminary period was 40 gm sugar utilization per insulin unit during February was 52 gm, during April, 66 gm.

Treatment and Course.—The patient was admitted on January 29, in coma with a blood sugar content of 445 mg and a carbon dioxide content of 11.8 per cent by volume. He was given 10 units of insulin before the results of the examination of the blood were learned. Then 30 units more were given, at noon the blood sugar had fallen to 273 mg and the carbon dioxide content had risen to 13.7. At 3 p.m., 20 units of insulin were given, and an hour later as he was still in coma 75 units were given. As the blood sugar had fallen to 208 mg and the carbon dioxide content had risen to 38.5 at 11 p.m., 50 more units were given with 20 gm of glucose. The total dose for the day was therefore 185 units. The following forenoon the boy was awake but restless and sweating. The blood sugar content was 77 mg and the carbon dioxide 5.2. Twenty gm of glucose were given, the blood sugar content rising by afternoon to 300 mg, and carbon dioxide to 57.6, when 3 units of insulin were given. The patient was fed during the day on oatmeal gruel. An interesting complication, the only one observed in our series was a hematuria, which we attributed to the cresol used in preserving the drug at that time, insulin-Lilly, H-5, containing 5 units per cubic centimeter, thus necessitating the injection of large amounts of fluid—37 cc in one day. As he was able to utilize in a preliminary period 40 gm of sugar, a daily dosage of 9 units increased to 30 in a few days rendered him sugar free by February 8, and he was finally stabilized on a diet of 2110 calories with 160 gm of available carbohydrate on 18 units of insulin daily. (See charts.)

Comment.—The foregoing case is interesting as illustrating a coma due to dietary excess in a child who previously had had good tolerance. Large doses of insulin were required to reduce the acid poisoning, and it is to be noted that even with the administration of glucose and orange juice a mild carbohydrate shock was produced at a blood sugar level of 77 mg, relieved by glucose solution. It is also of interest to note that in this case a blood sugar of 50 mg was unattended by symptoms. In this case also an infectious disease—German measles—is said to have preceded the onset of diabetic symptoms.

CASE 11—History.—A woman, aged 55, single, a seamstress, born in the United States, was admitted to the hospital in a coma on Jan 2, 1923. She died on Jan 3, 1923. No history was obtainable.

Physical Examination.—The patient had a well developed bronchopneumonia. Laboratory findings. There were 533 mg of blood sugar per 100 cc, the carbon dioxide tension was 10. Three hours before death the blood sugar content was 230 mg and the carbon dioxide tension 25.

Treatment and Course.—The patient was admitted in a coma at 8.30 p.m., dangerously ill with bronchopneumonia. Fifty units of insulin were at once administered, with 20 gm of glucose, the blood sugar was 533 mg, carbon dioxide, 10. As there was no improvement, 50 units were again given at midnight, and this dosage was increased by another 50 units at 4 a.m., at this time blood

sugar content was 440 mg. Fifty units were again given at 9 a.m. and 75 at 3 p.m., with a drop in the blood sugar to 230 mg and a rise in carbon dioxid to 25. The total insulin dosage was 275.

Necropsy—Necropsy revealed bronchopneumonia of the right middle and lower lobes, arteriosclerosis and fibromyoma uteri.

Comment—This case is of value as illustrating an excellent chemical result—a drop in blood sugar from 533 to 230, a rise in carbon dioxid tension from 10 to 25, with a great diminution of the ketonuria. Death, however, resulted from the pneumonia, which of course was in no way influenced by the insulin treatment.

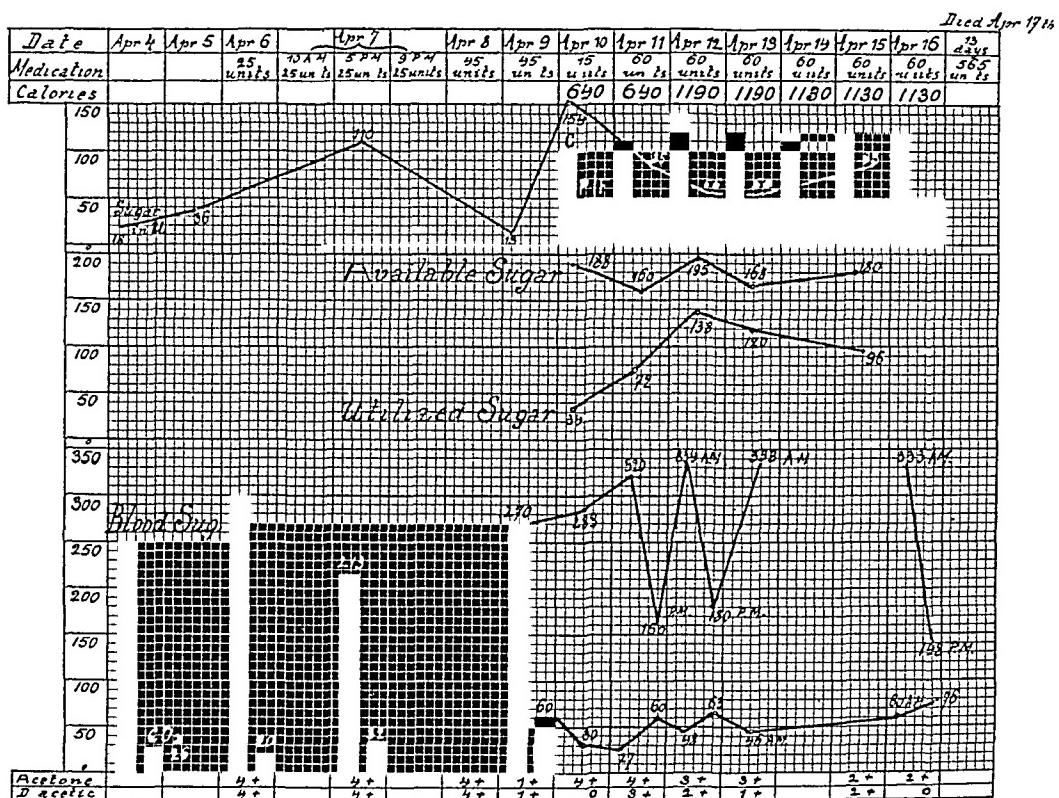


Fig. 14.—Data in Case 12

CASE 12—History—A man, aged 54, a letter carrier, born in Ireland, had had diabetes for five years. He was admitted to the hospital on May 1, 1922. He was discharged on June 17, 1922, on a diet containing 84 gm of protein, 84 gm of fat and 76 gm of carbohydrate. The patient was followed in the diabetic clinic. He was readmitted to the hospital on April 2, 1923, with a carbuncle of the neck which had started five days prior to admission. His past history was negative, except for bad teeth. His family history was negative.

Physical Examination—On the second admission he had a large carbuncle at the back of his neck, and a temperature of 103 F. A blood culture contained *Staphylococcus albus*.

Treatment and Course—The patient was admitted with a carbon tension of 26, which rose to 60 on April 9, and remained normal until he died. When first seen by the medical division he was given insulin, at first 25 units daily and then 45 and 60 units. While acidosis was rapidly relieved on this treatment

on a diet of 100 gm of carbohydrate, 50 gm of protein and later 50 gm of fat, he succumbed later to a blood sepsis. He was operated on April 4—a simple crucial incision and packing. He died on April 19, 1923.

Necropsy.—Necropsy revealed bronchopneumonia with multiple abscesses throughout the entire lung. The heart showed fibrinous pericarditis. The spleen was large, soft and of the septic type. Both kidneys contained a number of small abscesses.

Comment.—This case admirably illustrates chemical improvement without effect on the underlying infection.

CASE 13—History.—A man, aged 56, married, a tradesman, born in Germany, had had diabetes since 1910. He was admitted to the hospital on Nov 10, 1922. In January, 1921, his left toe became sore and later black. His left foot was amputated at the lower third of the tibia, in September, 1921. The right toe became sore in May, 1922, and black in December, 1922. He had had no infectious diseases. His teeth started to decay rapidly about 1910, when diabetes started.

Physical Examination.—Examination revealed an enlarged liver, a gangrenous toe and marked arteriosclerosis. His left leg had been amputated at the lower third of the tibia.

Treatment and Course.—He was put on insulin treatment on Jan 4, 1923, to Jan 18, 1923, when it was stopped because of the low supply. Insulin treatment was started again on March 5, and continued until March 31. His weight on January 4, was 110 pounds (49.89 kg) and it is now 117 (53.07 kg). The gangrenous toe of his right foot is about ready to fall off.

Comment.—This case of diabetes was of long standing, but on a maintenance diet of 1,760 calories the patient was maintained sugar free. He was put on insulin treatment with the idea of performing a surgical operation. His reaction to insulin, however, was less marked than in any case in our series, 1 unit enabling the utilization of only 0.9 gm of glucose. As it was decided that it was better to permit his gangrenous toe to slough off than to amputate above the knee, he was put back on his maintenance diet, and is still in the hospital.

COMMENT

In our series there have been six cases of diabetic coma, only one uncomplicated by an infection. Infections whose course lasted for twenty-four hours were all influenced chemically by insulin treatment, but the patients succumbed to the infection, with the exception of the patient with pneumonia reported above (Case 9), who made a perfect recovery, and is now sugar free. The patient with the uncomplicated case recovered, making a percentage of recovery in the series of 33½%.

Of the series, there is a history of diabetes immediately after an acute infection in six cases. The cases of the three children in Case 7 are particularly striking, and followed an infectious jaundice. Case 10 followed measles and Case 1 a tooth infection. It has long been recognized that an acute infection causes a rapid exacerbation of diabetic symptoms, but we feel that the possibility of diabetes resulting from the

loss of the pancreatic function secondary to an infection has been neglected, and urge the collection of data on this point. Epithelial gland infections following the ordinary infectious diseases of childhood are common enough phenomena, as for instance orchitis in mumps.

SUMMARY

- 1 Insulin treatment will invariably raise the carbohydrate tolerance both in mild and in severe diabetes.
- 2 Acidosis even in its severe form of coma can often and perhaps usually be controlled, if uncomplicated by infection.
- 3 In certain instances the pancreatic function seems not only to be spared, but also to be increased by insulin treatment.
- 4 Hypoglycemia, while a real danger, can readily be guarded against and overcome by balancing the diet against insulin administration.
- 5 Diet must be more carefully maintained than in the case untreated by insulin.
- 6 Education of the patient, both in the calculation of his diet and the simple analysis of his urine, and in the symptoms of hypoglycemia, must be insisted on. This procedure is by no means as difficult as it appears, and any ordinarily intelligent person can be sufficiently instructed.

CLINICAL STUDIES OF DIGITALIS

I EFFECTS PRODUCED BY THE ADMINISTRATION OF MASSIVE DOSAGE TO PATIENTS WITH NORMAL MECHANISM¹

DREW LUTEN, MD

ST LOUIS

It has long been known that the administration of digitalis to patients with heart disease produces striking clinical improvement in many cases. Students of cardiology have long been occupied with two closely related problems (*a*) a differentiation of those cases that are improved, from those that are not benefited by the drug, (*b*) an explanation of its action, and an understanding of the manner in which it produces improvement. Little progress was made toward a solution of these problems until recent years, and even now, although advancement has been rapid, no more than a fair beginning has been made.

A few facts have been established. It is well known that digitalis causes considerable delay in auriculoventricular conduction in many patients, and careful studies² have indicated that prolongation of a-v conduction of greater or less degree is a constant effect of the drug in all cases. The exact mechanism by which this depression of conduction is brought about, or rather the degree to which the contributing factors are responsible, is not yet completely understood in all its details. That it is, however, responsible for the ventricular slowing which is produced by the administration of digitalis to patients with auricular fibrillation and rapid ventricular rate, there seems to be little reason to doubt. That this ventricular slowing by prolonging diastole, both relatively and absolutely, results in increased cardiac efficiency, can hardly be questioned, for slowing parallels improvement in symptoms, and on withdrawal of the drug, increased ventricular rate is attended by a recurrence of the symptoms of impaired circulation. There is, then, general agreement that digitalis causes improvement in patients with auricular fibrillation by producing ventricular slowing through a depression of a-v conduction, thus allowing the ventricle more rest. But is this the sole factor in the improvement in such cases? Is there any other action of the drug that exerts a favorable influence in cases of auricular fibrillation, in addition to its action on the conducting tissues by virtue of which it produces slowing of the ventricle?

* Read before the Saint Louis Medical Society, May 22, 1923.

* From the Department of Internal Medicine, Washington University School of Medicine.

1 Cohn, A. E. Clinical and Electrocardiographic Studies on the Action of Digitalis, J. A. M. A. 65: 1527 (Oct 30) 1915.

Robinson,² in estimating the rapidity and persistence of the action of digitalis on hearts showing auricular fibrillation, based his conclusions entirely on the occurrence of ventricular slowing and made this the sole criterion in his determinations. No other evidence of any beneficial action can be so readily demonstrated on patients. No other criterion of effect can be so easily applied as a determination of changes in rate. Lewis³ finds no evidence of any "other important action of the drug on the human heart" and attributes the beneficial effect of digitalis in such cases solely to the slowing of the ventricle through depression of a-v conduction.

This view takes no account of any favorable action of the drug directly on the ventricular muscle, and *limits the therapeutic use of digitalis, generally speaking, to cases that exhibit fibrillation of the auricles.* MacKenzie⁴ holds practically the same opinion, although he thinks that in cases of heart failure which are not associated with auricular fibrillation, digitalis should be tried, since "we are forced to try all sorts of remedies" and "drugs of the digitalis group offer the best prospects."

Directly opposed to this view is the opinion held by most clinicians and by certain eminent investigators. Eggleston,⁵ Pratt,⁶ Christian,⁷ and West and Pratt⁸ have all noted evidences of favorable action from the administration of digitalis to patients with normal rhythm.

In view of such diversity of opinion, then, the question of the beneficial effect of digitalis in patients with normal cardiac mechanism seemed to demand further study. Particularly was this true since the problem is attended by difficulties greater than are encountered in a study of its action in auricular fibrillation, and since an accurate estimation of its effects in patients with normal mechanism is more difficult to reach. It is evident that no benefit in cases with normal mechanism can be expected to result generally speaking from that action of digitalis to which is usually ascribed its beneficial result in fibrillation of the auricles. No depression of a-v conduction will produce ventricular slowing in cases with normal mechanism (unless heart block be induced), and any effect on the musculature that might increase the

2 Robinson, G C. The Rapidity and Persistence of the Action of Digitalis on Hearts Showing Auricular Fibrillation, Am J M Sc **159** 121 (Jan) 1920

3 Lewis, Sir Thomas. On Cardinal Principles in Cardiological Practice, Brit M J **2** 621 (Nov 15) 1919

4 MacKenzie, Sir James. Principles of Diagnosis and Treatment in Heart Affections, Oxford Medical Publication, 1918

5 Eggleston, Cary. Digitalis Dosage, Arch Int Med **16** 1 (July) 1915

6 Pratt, Joseph H. Digitalis Therapy, J A M A **71** 618 (Aug 24) 1918

7 Christian, H A. Digitalis Therapy, Satisfactory Effects in Cardiac Cases with Regular Pulse Rate, Am J M Sc **157** 593 (May) 1919

8 West, H F, and Pratt, Joseph H. Clinical Experience with a Standardized Dried Aqueous Extract of Digitalis, J A M A **75** 77 (July 10) 1920

efficiency of the ventricle is difficult to measure. Dependence must be placed on any indirect evidence of benefit that may be shown in these cases. The effect of any coincident factor whose influence is known to be favorable, such as rest in bed, must be eliminated.

The value of most of the clinical studies that have been made of the problem has seemed to be impaired by the failure of the investigators to supply sufficient quantitative estimations of the beneficial effects of rest. In order to justify the conclusion that any improvement that follows the administration of digitalis is due to the action of the drug, there must be a clear idea of the patient's *rate of progress* before the drug was given, and it must be shown that this rate of improvement was accelerated after the administration of the drug. Quantitative data must be supplied rather than the impressions obtained by the investigator. A statement of the output of urine or of the exact heart rate before the patient was given digitalis, and similar data for the period following, carry more conviction than the mere statement that diuresis or that slowing did or did not occur.

It appeared that data of this sort were inadequate in most of the studies referred to above that indicate a beneficial action of the drug, particularly in view of the opposite opinion held by so eminent a student as Sir Thomas Lewis. In administering digitalis to patients with regular heart action, little evidence of improvement had ever come under my observation which could not reasonably be explained without the assumption that it was due to the action of the drug. This fact and the weight of opinion expressed by Lewis and MacKenzie inclined me to believe that digitalis is of no value in patients with normal mechanism. It was determined, however, to attack the problem with as little as possible of preconceived opinion.

The main object has been to determine (a) whether there is any evidence that digitalis has a favorable action on patients with heart disease other than those with auricular fibrillation (or flutter). If evidence of such an effect should be exhibited, further problems would be (b) to note exactly just what are the results of such action, (c) to determine, if possible, what classes of patients with normal rhythm are so affected by the drug, and finally, (d) to seek an explanation of the mechanism by virtue of which such effects are produced.

METHOD OF STUDY

The present study was conducted as follows. Patients with normal cardiac mechanism who showed evidence of decompensation or symptoms that might be accounted for either in whole or in part on that basis, were put to bed and given a restricted diet, a measured amount of fluid, and no drug that might affect the heart or kidneys. This was continued for a period of one, two or more weeks. At the beginning of this period

of observation the condition of the patient was determined as accurately as possible, and the findings noted in his record. Particular care was taken to note the heart findings, evidence of congestion of the lungs, hydrothorax, size of the liver, amount of edema, body weight, amount of urine, electrocardiogram, vital capacity, blood pressure, nonprotein blood nitrogen, urine findings and the patient's symptoms. A Wassermann test was made on the blood of all patients. None had continuous fever.

During this preliminary period frequent observations were made along the lines mentioned above, and at the end of the period a summary was entered in the record which gave the results of rest in bed and the patient's progress while at rest. This was expressed in graphic form when practicable, showing in this way any tendency toward improvement, or the reverse, and the *rate* of progress.

The length of this period of observation was determined by the special circumstances in each case. After a satisfactory estimate of the effect of rest could be made, the observation period was terminated, and, without changing any other factor, a large amount of digitalis was given in a short period of time. Observations were then continued in the same manner as before. Any pronounced changes which resulted could reasonably be attributed to the administration of digitalis. The graphs were particularly valuable in determining *any change in rate* of progress.

The digitalis used was a stock tincture which has repeatedly been shown to possess a high degree of potency. It was not restandardized. No arbitrary rule was followed in determining the amount to be administered. In general, an estimate was made of the total dose as determined by the Eggleston method for an average tincture, and an amount somewhat smaller than this estimated dose was chosen. This was done because experience with the tincture used had shown that its potency was high. This "chosen dose" was administered in divided doses, usually about one half being given at once and smaller portions administered at intervals for the next twelve to twenty-four hours. If nausea or other evidence of toxic action appeared, the drug was stopped.⁹ In no case was a large amount given to a patient who might have received digitalis within three weeks.

The records of pulse, weight and urine output were made by the nurse. Those of blood pressure and vital capacity were made by the clinical clerk assigned to the case. Notes on the heart, size of the liver, amount of edema and patient's symptoms, together with the summary at the end of the observation period, and a similar note after the administration of digitalis, were made by myself.

⁹ One patient (Case 9) received an additional dose after nausea and vomiting. This case receives comment below.

About forty patients were studied. In many cases certain quantitative observations were not made, and some of the results, therefore, are equivocal because of insufficient data. Such cases are not included in this series. The series does include, however, every case record which contains data sufficient to warrant a conclusion as to the effect of digitalis in the individual case irrespective of any result that might have been anticipated from observation of similar cases. The records of twenty cases are thought to be complete enough to satisfy this condition. Incomplete cases are excluded irrespective of any result that might have been suggested by the incomplete data recorded. It may be stated here that these discarded records are of great value in that the evidence which they give is strongly confirmatory of the soundness of the conclusion arrived at from a study of those cases whose records are more complete, and which are recorded below.

RESULTS

In order to save space and to make convenient a comparison of the records before and after the administration of digitalis, these twenty case records are given in tabular form. The table (Table 1) gives the record of each patient as follows. In the first column are shown the case number, age, Wassermann reaction, and diagnosis. Column two gives the physical signs on examination of the heart and the electrocardiographic findings. Column three gives, in order, the number of days in hospital, hospital result number of days the patient was kept under observation before digitalis was administered, the amount of the tincture that was given and the number of hours over which the administration of this amount of the drug was distributed. In the fourth column are noted the evidences of digitalization. Following this are recorded the patient's symptoms pulse rate, amount of edema, vital capacity, size of liver weight, renal tests, etc., amount of urine blood pressure, and "remarks." The three parallel columns give such record on admission O A, for the observation period, O P, and for the period after the administration of digitalis, A D.

The records of these twenty cases, selected solely on the basis of completeness of data, give an unmistakable answer to the main problem at hand. Digitalis affected most of these cases favorably. The favorable effects included diuresis (with attendant loss of edema, decrease in the size of the liver and loss of weight), rise of vital capacity and improvement of symptoms. In many cases these results were most impressive.

The accompanying figures, which reproduce some of the records given in the table, give these results as far as practicable, in graphic form, and thus show the effect of digitalis on the *rate of progress*. The effect on symptoms, which was often most striking cannot, of course, be represented in this way.

TABLE 1—Data Shown

Case Number Age Wassermann Test Diagnosis	Heart Electro cardiogram	Days in Hospital Result Observed Digitalis	Evidences of Fleet	Symptoms	Pulse Rate		
					Extremes	Mean	Trend
1 50 years Negative Chronic myocarditis, arteriosclerosis, decompensation	Sounds weak Left ventricle predominant, T upright in all	22 days	T negative in all left ventricular premature con- tractions 7 days 20 c.c. 9 hours	O A	Cheyne Stokes sign, dyspnea, nausea		
		Improvement		O P	No improvement, Cheyne Stokes' sign	83-123	100
		7 days		A D	Sudden improve- ment, no Cheyne Stokes' sign	(3) 68-102 (6) 60-90	86 78
2 22 years 4 plus Aortic insufficiency, decompensation	To and fro murmur at aortic Normal	39 days	None	O A	Dyspnea, cough pain in chest		
		Improvement		O P	Marked improve- ment	88-120	100
		8 days		A D	Progressive improvement	(4) 85-108 (4) 72-100	95 86
3 61 years Negative Chronic myocarditis chronic nephritis decompensation	Systolic at apex T negative in I R notched in II	23 days	Nausea, vom- iting, T low- ered in I II and III ven- tricular extra systoles 13 days 21 c.c. 12 hours	O A	Dyspnea, weakness		
		Improvement		O P	Considerable improvement, no dyspnea	60-105	90
		13 days		A D	More rapid improvement	64-96	82
4 54 years Negative Chronic myocarditis, chronic nephritis premature contrac- tions A and V decompensation	Sounds distant T iso electric in I and II	59 days	Increase in number of premature contractions A and V	O A	Dyspnea		
		Died		O F	Fluctuated	75-105	90
		17 days		A D	Fluctuated	65-105	88
5 39 years 4 plus Aortic insufficiency, chronic nephritis nephritis (syphilitic), decompensation	Diastolic at left sternal border sys- tolic and diastolic at apex	33 days	Nausea vomiting, premature contrac- tions	O A	Swelling of abdo- men, dyspnea orthopnea		
		Died		O P	Improvement	60-130	92
		10 days		A D	Fluctuated	80-100	85
6 43 years Negative Aortic insufficiency, chronic myocarditis, decompensation	T negative in I and II P R, 0.2	20 days	Nausea vomiting T lowered in I II and III P R, 0.23	O A	Dyspnea, pal- pitation		
		Improvement		O P	Improvement	(7) 75-112 (3) 70-88	90 80
		10 days		A D	Progressive improvement	60-90	78
7 23 years Negative Chronic valvular disease, mitral stenosis and insuffi- ciency, premature contractions decompensation	Diastolic rumble and thrill at apex, bigeminy fibrillation (auricular)	67 days	None	O A	Cough, dyspnea, palpitation, dizziness		
		Improvement		O P	Very slight im- provement, normal mechanism	112-140	120
		33 days		A D	Decided im- provement	112-132	120
8 44 years Negative (14 cells, spinal fluid) Aortic insufficiency, chronic (syphilitic) myocarditis arterio- sclerosis, decom- pensation	To and fro murmur at aortic left sternal bor- der and apex T negative in II and III	22 days	Nausea (toxic rhythm) interpretation? T lower in III	O A	Pain in epigas- trium, dyspnea, nausea, cough	80	
		Improvement		O P	Marked im- provement	68-96	78
		10 days		A D	Improvement (progressive) after toxic	72-90 *(95)	82

The numbers in parentheses at the left give the number of days over which observations were made. Parentheses at pulse after digitalis administration, for three days were 68 to 102, mean 86, for six days, 60 to 90 mean 78. The weight

Case Records in Brief

Tremor	Vital Capacity, Cc	Liver (Cm Below Cost of Margin)	Weight, Kg	Other Findings	Amount of Urine, Cc	Blood Pressure			Remarks
						Tremors	Mean	Tendency	
Slight		15	86.3	PSP 15%, NPN, 57.8, Alb, 4 gm		190 — 150			Result as striking as ever seen in auricular fibrillation
None	2,750 (2) 2,900 (1) 3,000 (0)	10 (4) 8+ (0)	88 (0)	Less albumin and casts	340-1,140	172-196 — 132-160	185 — 145		
None	3,935 (5) 4,400 (10)	Rapid decrease	77.6 (2)		4,700 (1)	190-210 — 105-160	Sup — D down		
Moderate		14 (?) 9 (?)	68.6						Improvement progressive, not definitely influenced by digitalis
None		4	74.7	PSP, 90%, NPN, 38	About 700 per day	120-170 — 30-60	125 — 40	down — down	
None		4	?		About 700 per day	140 — 20	1st day, then slow fall		
Marked		10	113	Trace albumin, PSP 40%, NPN, 42.7					Rapid decrease in liver, diuresis, loss of weight, improvement in symptoms
Diminished	Rose from 1,400 to 2,500 in 8 days	8 (2)	95	PSP 65%, NPN, 36	About 850 per day	140-115 — 95-70	120 — 85	down — down	
No note	Continued rise to 3,200 in 5 days	3? (1) 4? (1)	93 (1)		1st 12 hours not collected "an awful lot" 2d 12 hours 1,100	150 — 85	1 day, rapid fall		
Marked	733	9½	84.5	Alb and casts PSP, 40%, NPN, 60	Urine not accurately measured	130 — 110			Evidence of pulmonary thrombosis at time of digitalis administration
Slight decrease	716 to 1,230	8	81.5 (1)			120-134 — 100-105	128 — 103	down — down	
No change	675 to 1,160	8	80 (20)		No apparent increase	210 — 175			
Moderate	1,100	9¼		Alb and casts PSP, 20%, NPN, 41		145 — 65			Began to lose ground five days after digitalis
No change	1,050 to 1,100	6¾			About 500 per day				
Fluctuated	1,000 to 1,200	Slight progressive decrease			About 600 per day				
Moderate		10	85	Alb and casts NPN, 35.7		165 — 87			Measurements do not show when liver decreased, use of vital capacity
None	1,100 (6) 1,200 (3) 1,150 (2)	No note	80.6 (3)		About 700 per day				
None	1,300 (1) 1,700 (5)	Not enlarged	76.3 (4)		About 700 per day				
Marked	450	11		NPN, 76					Question of previous digitalis poisoning, lertotoxic with subsequent improvement
Same	450 to 550 450 (1)			NPN, 33		95 — 80	(3)		
Much less	700 (3)	8½(7)							
Moderate	1,300	8	68.4	Slight albumin, PSP 55%, NPN, 36		160 — 90			Relieved of symptoms under rest no definite effect from digitalis, toxic rise in blood pressure
None	Rose to 2,900 in 7 days	0	63 (2) (In 7 days)	No albumin	About 600-1,200	160-120 — 90-70	Down — Down		
None	Rose to 3,100 in 5 days	0	61.4 (0) 59 (2)	Faint trace of albumin (2) (3)	About 450-1,160	130 — 90	Down — Down		

The right show the day on which the accompanying observation was made that is, in the first case, the extremes of on the day of administration was 88 kg two days after digitalis weight was 77.6 kg * indicates isolated observation

TABLE 1—Data Showing Case

Case Number Age Wassermann Test Diagnosis	Heart Electro cardiogram	Days in Hospital Result Observed Digitalis	Evidences of Effect		Symptoms	Pulse Rate		
						Extremes	Mean	Tendency
9 52 years (II) Negative Chronic myocarditis, chronic nephritis, arteriosclerosis decompensation	First sound prolonged at left sternal border R notched in I, T nega tive in I P R 0 2	94 days Died 7 days 17 c.c., 25 hours	Extreme nausea some vom iting dis comfort auriculo ventricular dissociation auricular, 131, ventricular, 162, change in ventricular complex	O A O P A D O A	Slight dyspnea nausea and vomiting			
					Little, if any, improvement	(2) 78-110 (4) 72-90	80 80	Down No
					(2) Worse			
					(8) Some improve ment	*(60) 70-100	81	
10 53 years Negative Chronic myo carditis, mural thrombi left and right ventricles, de compensation	Systolic at apex P R 0 16 QRS, 0 11 T negative in I	108 days Died 7 days 10 c.c., 10 hours	P R 0 2	O A O P A D O A	Dyspnea, palpita tion, Cheyne Stokes' sign	105		
					Slight improve ment, Cheyne Stokes' sign	(5) 58-108 (2) 80	95	Down
					Improvement in dyspnea, Cheyne Stokes' sign	70-110	78	
11 63 years Negative Emphysema, chronic bronchitis arterio sclerosis	No abnormal heart find ings Electrocar diogram normal P R 0 18	83 days Improve ment 16 days 11 c.c., 5½ hours	Nausea and vomiting T lower in III (%)	O A O P A D O A	Long attacks of coughing dyspnea			
					Slight im provement	74-100	85	
					No improvement	72-96	85	
12 57 years Negative Chronic nephritis chronic myocarditis arteriosclerosis	First sound impure at apex 2d sound redupli cated	31 days Improve ment 16 days 10 c.c. 7 hours	Nausea and vomiting T lower in II	O A O P A D O A	Dyspnea, weak ness, headache nausea, vomiting			
					Stronger less dyspnea no vomiting	(5) 78-140 (11) 72-95	82 85	Down
					Progressive improvement	72-93	82	
13 52 years (II) Negative Chronic myo carditis, chronic nephritis decompensation	Soft systolic at apex sounds faint left ventricular premature contractions T iso electric in all	35 days Improve ment 16 days 21 c.c. 24 hours	Nausea and vomiting P R length ened 0 05 R less shaded	O A O P A D O A	Dyspnea weak ness, insomnia	70		
					(9) Improvement	*(120) 78-108	90	No
					(7) Stationary	*(60) 70-105	80	
					Improvement	(4) 62-96 (7) 68-90	78 76	
14 46 years Negative Chronic myo carditis, chronic nephritis decompensation	Front systolic all are is gill low complexes low T negative in I and III	35 days Improve ment 8 days 16 c.c., 16 hours	Vomiting, A V disso ciation rapid A and V ectopic beats bi geminy	O A O P A D	Dyspnea, dizz iness, palpitation			
					Some improve ment still severe	78-120	90	No
					Much nausea rapid improve ment after 7 days	(2) 75-120 (3) 85-105 (10) 72-95	95 87	

Records in Brief—(Continued)

Edema	Vital Capacity, Cc	Liver (Cm Below Costal Margin)	Weight, Kg	Other Findings	Amount of Urine, Cc	Blood Pressure			
						Extremes	Mean	Tendency	
Marked		12 ?		Albumin, 2 plus, PSP, 10% NPN, 62		230 130			Toxic with delayed diuresis and loss of weight and rise of vital capacity
Moderate	2,900 (1)	12½ (1)	84 (0)	NPN, 54 (2)	1,100-1,600 1,350 no tendency	230 210 215 140 110, 130			
Moderate	3,000 (1) 3,000 (2)	6¾ (2)	83 (1) 82 (2)		400 700	140 190 100 (1), 120 (2)			
None	Rise to 3,600	6¾ (3) 8½ (10)	82 (3) 73 1 (10)	NPN, 53	1,600-4,300 2,851	260 210 120 (3), 135 (10)			
Slight	2,000	7	66	Trace albumin, NPN, 50		160 88			
None	2,100 (1)	7½ (4) 4½ (0)	72 6 (1)	Trace albumin NPN, 45 (1)	(3) 500-850 (3) 1,150-1,200	152-110 158 98-100 100			
None	2,000 (1) 1,900 (4) 2,100 (7)	0 (4)	67 (1) 64 (2)	No albumin (3), NPN, 40 (4)	3 100 (1) 1 725 (2)				
None		3		No albumin, PSP, 65%	*	160 90			
None	2,800 (4) 2,700 (2)	3	48 1 (4) 48 6 (0)	No albumin NPN, 34		(7) 115-130 118 70-95 80			
None	2,750 (2) 2,800 (5) 2,900 (7)		46 8 (2) 46 8 (8)	No albumin		155 85 (1)			
None		6		Albumin, PSP 26% NPN, 66					Temporary rise of blood pressure only definite effect, rise of vital capacity?
None	1,200 (14) 1,600 (9) 1,675 (1) 1,850 (0)	6 (1)	48 1 (5)	Less albumin, NPN, 43	450-1,000	(7) 196-215 100-105			
None	1,950 (1) 2,000 (3) 1,950 (5) 1,700 (7)		50 (1) 50 4 (7)	Continued less albumin	No apparent change	230 112 (1)			
Marked	1,650	11½	109 1 (14)	Trace albumin PSP, 30%, NPN, 43		120 90			
Moderate	Rose to 2,500	8½ (8)	98 7 (6)	Trace albumin	500-1,000 average 800	120-135 125	No		
Moderate	2,600 (6) 2,400 (1)	8 (1)	98 4 (0)	Moderate albumin	600-925 average 700	90-95, 90	No		
None (4)	2,500 (2) 3,400 (7) 3,600 (10)	8 (1) 7 (3) 7 (17)	93 1 (1) 88 6 (2)	Trace albumin	2,000 in 2d 12 hours 2,350 (4)	135 (0) 140 (1) 90 90			
Moderate	800			Albumin plus, PSP, 5%, NPN, 45					
Moderate	Rose to 1,200 (0)		80 3 (3) 85 4 (0)	Less albumin	500-1,150 average 600 no tendency	115-132 125 95-110 105	No		
Rapid disappearance	1,150 (3) 1,200 (6) 1,400 (10) 1,200 (14)		75 (4)	Albumin declined with diuresis	3,200 (1) 1,900 (2)	140-155 (8) 105-116			

rose at 8 p.m., diuresis that night, toxic delayed symptomatic improvement

TABLE 1—Data Showing Case

Case Number Age Wassermann Test Diagnosis	Heart Electro cardiogram	Days in Hospital Result Observed Digitals	Evidences of Effect		Symptoms	Pulse Rate		
						Extremes	Mean	Tendency
15 46 years Negative Chronic nephritis chronic myocarditis, arteriosclerosis, decompensation	Low systole at aortic and apex, gallop few premature contractions	27 days Improvement	Nausea and vomiting	O A	Dyspnea, cough, weakness dizziness			
		7 days 14 c.c., 24 hours		O P	Improvement in dyspnea and cough	85-120	102	No
				A D	Rapid improve ment	(3) 84-108 (4) 72-100	94 80	No Down
16 39 years Negative Chronic nephritis adenoma of kidney, atheroma of coronary, chronic myocarditis	Soft systolic at apex, A second impure T negative in I and II	40 days Died	Nausea and vomiting	O A	Headache fail ing vision			
		19 days 15 c.c. 10 hours		O P	Marked im provement	(12) 80-112 (7) 80-93	94 86	Down No
				A D	Continued to feel well	76-98	86	
17 40 years 3 plus Syphilitic myocarditis aortitis, decom pensation	Loud systolic at apex and base T negative I, II and III	44 days Improvement	Disappear ance of nausea	O A	Dyspnea vom iting pain in epigastrium			
		7 days 18 c.c., 23 hours		O P	No improve ment	(1) 74-98 (3) 74-97	82 86	No
				A D	Less dyspne, less nausea	(2) 73-100 (4) 80-90	86 86	
18 48 years 4 plus Chronic (syphilitic) myocarditis arterio sclerosis decom pensation	Systolic at apex dia stole at aortic two weeks after digi talis T negative in I, QRS 0.12 in II and III	32 days Improvement	Nausea and vomiting T lowered in I, nega tive in II	A O	Dyspnea, cough, weakness			
		7 days 10 c.c., one dose		O P	No improvement Cheyne Stokes sign developed	84-100	90	No
				A D	Prompt relief of all symptoms	(2) 78-90 (3) 72-78	82 70 63	Down Down
19 43 years Negative Chronic myocarditis, chronic nephritis, dilatation of aorta decompensation	Systolic at all veins	14 days Improvement		O A	Pain in abdomen and chest, dysp nea, insomnia			
		9 days 12 c.c., 24 hours		O P	Some improve ment	(5) 68-106 (4) 68-90	100 80	Down Down
				A D	Rapid improve ment	65-80	78	
20 57 years Negative Chronic myocarditis chronic nephritis, decompensation	Soft systolic at apex T negative in I and II P.R. 0.2 R shaded	24 days Improvement	Nausea and vomiting T lowered in I	O A	Dyspnea, cough pain in epigas trium			
		7 days 13 c.c. 17 hours		O P	Some improve ment	60-76	68	Up
				A L	Rapid improve ment	66-80	72	

Records in Brief—(Continued)

Edema	Vital Capacity, Cc	Liver (Cm Below Costal Margin)	Weight, Kg	Other Findings	Amount of Urine, Cc	Blood Pressure		
						Extremes	Mean	Tendency
None	1,650	5 1/4		Albumin plus, casts, RBC, PSP 15%, NPN, 67		210 — 130		
None	Fell to 1,400 (0)	5 1/4	73.1 (0)	Less albumin	650-1,000 no tendency	222-195 140-124 — 215 135	215 — 135	No Up
None	2,300 (1) 2,500 (1) 2,500 (5)	2 3/4 (2) 0 (7)	70.4 (2)		1,500 1st 12 hours	(5) 230-250 — 150-205		
None	2,200	0		Albumin, 10 gm, PSP, 10%, NPN, 111			225 — 155	No effect except nausea, suggestive fall of blood pressure
None	2,600 to 2,900 2,800	0	64.3 (0)	Albumin, 2.5 gm, NPN, 95	1,300-2,400 average 2,200	(10) 185-190 — 135-140		
None	2,600 to 2,900 2,800	0	63.6 (5)		(5) 750-1,100 (intake smaller)	(2) 170-175 — 118-135 (3) @ 180 — 125		
"None"	900	8		Albumin plus, PSP, 37%		145 — 70		Progressive fall in blood pressure
"None"	1,000 (5) 900 (3) 800 (0)	9 (1)	80.8 (2) 81 (0)			110-160 — 70-80	Down — Down	
1 to 1.5 cm decline in measure	700 (1) 850 (1) 900 (5)	6 (6)	75 (4)			190-140 — (7) 55-70		
Moderate		10		Albumin plus, PSP 40%, NPN, 32				10 c.c. at 8 p.m. diuresis that night, no morphin for first night in a week, remarkable immediate result
Moderate (same)	1,700 (5) 1,900 (4) 1,700 (2) 1,900 (0)	8 1/4 (0)	81.5 (4) 81.5 (0)		300-800 average 500 no tendency	182-195 — 120-142 188 — 130		
None (3)	2,100 (2) 2,500 (3) 2,700 (4) 2,900 (6)	0 (3)	79.6 (1) 74.5 (2) 72.7 (3)	Trace albumin (15)	5,200 (1) 2,600 (2)	190 — 125 155 — (2 and 12) 10		
Slight		"At umbilicus"	68.2	Albumin plus				Average result
A little less	2,900 (4) 2,700 (3) 2,500 (0)	6 (0)	69.2 (1) 68.2 (0)	Less albumin	375-850 average 600 no tendency	135-140 — 105-115	No — No	
Much less (1), none (5)	2,800 (1) 3,000 (2) 3,200 (3)	4 1/2 (2)	67.4 (1) 65.6 (2) 64.3 (4)		2,600 (1) 1,950 (2)	155 — (0) 125 150 — (1) 115		
Moderate		11	76	Much albumin casts, NPN 45% PSP, 70%		2.0 — 0.5		Average result
Some diminution	1,900 (6) 2,000 (3) 2,300 (1) 2,400 (0)	9 (0)	75 (1) 74.6 (0)		525-1,400 average 800 no tendency	230-185 — 95-85	Down — No	
Rapid diminution	2,500 (1) 2,700 (2) 2,500 (4)	5 (2) 0 (3)	75 (1) 72.1 (2)		2,200 (1) 3,450 (2)	215 — (1 and 2) 85 180 — 85		

Figure 1 thus represents graphically the data recorded for the eighth case of Table 1. In this, and in the other figures, the solid dots represent systolic blood pressure, the smaller rings, diastolic blood pressure, the larger rings connected by the heavy broken line, vital capacity expressed in cubic centimeters, the blocks, weight in kilograms, the vertical columns at the base, urine in cubic centimeters, the horizontal lines, mean pulse rate, "L" represents the extent of the liver in centimeters below the costal margin in the midclavicular line, and the dotted column shows the time of digitalis administration.

It will be noted that during ten days' rest there was a fall in blood pressure and in weight, a decrease in size of the liver, and a rise in vital

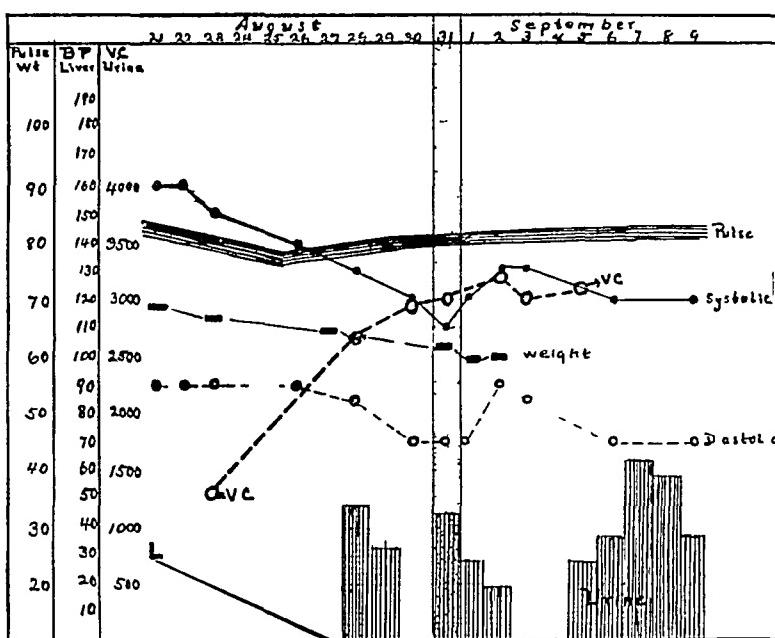


Fig 1 (Case 8) —Effect of rest

capacity. If digitalis had been given at the time this patient was put to bed, improvement might easily have been attributed to the drug. There is, however, little evidence that he was favorably affected by it.

Figure 2, which reproduces the record of the third case of Table 1, shows loss of weight and rise of vital capacity after digitalis administration, but at a rate which was not changed by the drug. It will be observed, however, that the liver, which after an initial diminution had remained stationary in size previous to the administration of the drug, underwent a rapid further shrinkage subsequent to digitalis administration.

A similar, though less rapid, effect on the liver is shown in Figure 3 (tenth case of the table).

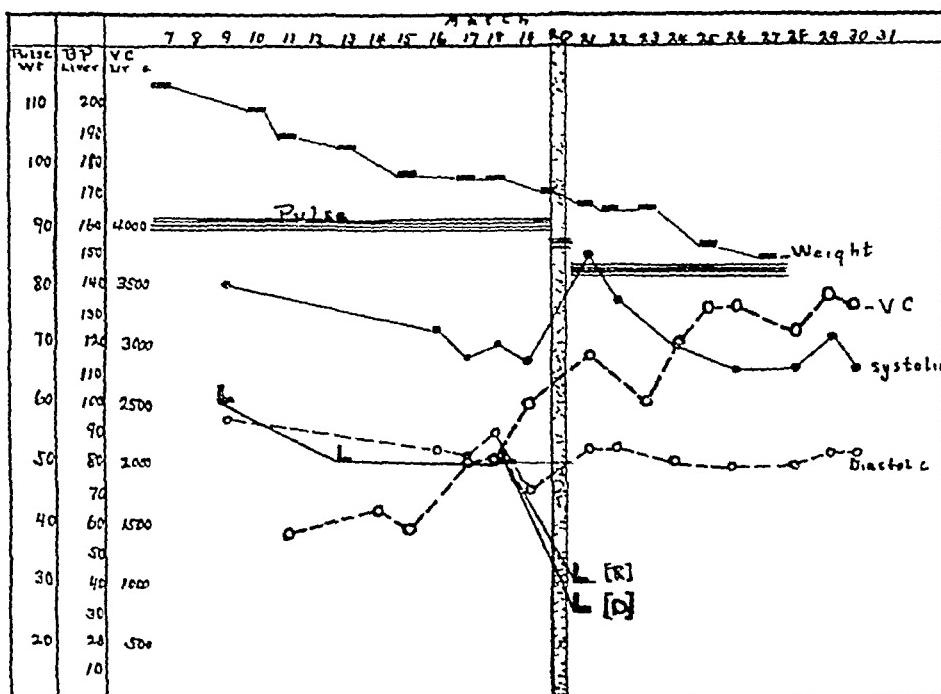


Fig 2 (Case 3) —Principal effect on liver R indicates resistance, D dulness

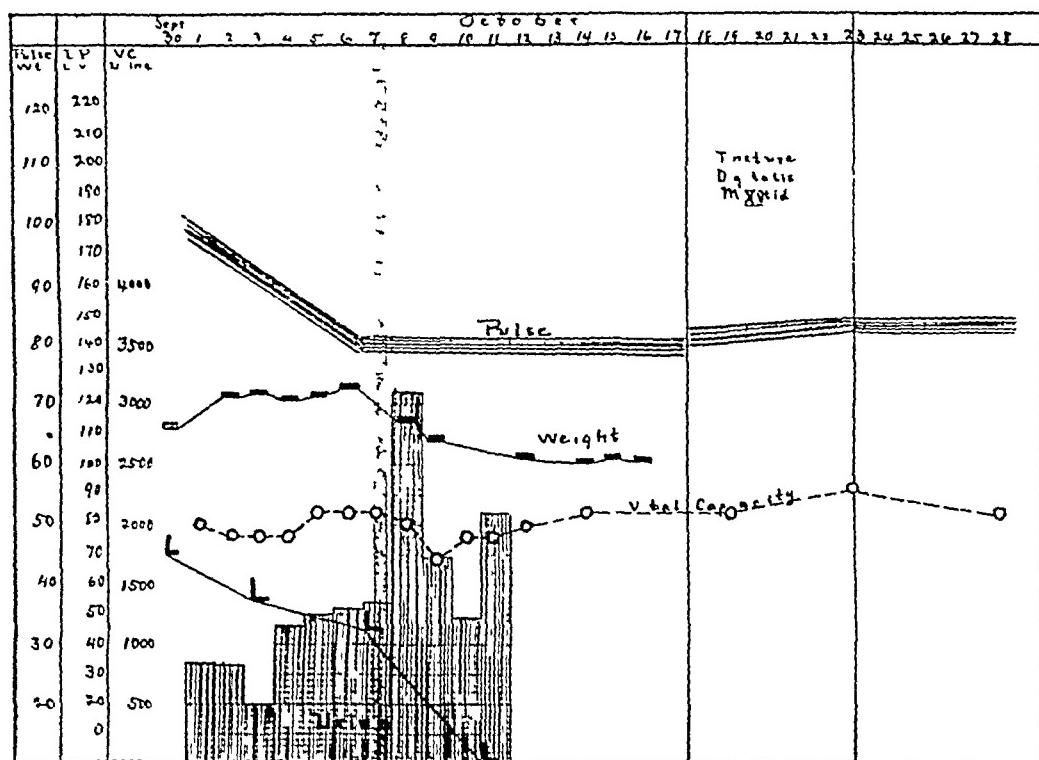


Fig 3 (Case 10) —Diuresis loss of weight, no rise of vital capacity

This patient showed also a considerable diuresis and loss of weight, but without an increase in vital capacity. It will be noted that the pulse rate, which had steadily declined during the observation period, showed no further fall at the time of the diuresis and symptomatic improvement.

Figure 4 (Case 1 of Table 1) shows a loss of 10.4 kg in weight in two days, with a diuresis of proportional extent. The most striking results in this patient cannot be represented graphically. The decrease in thickness of the liver was remarkable. This organ had presented a visible tumor which had diminished a little in size during observation

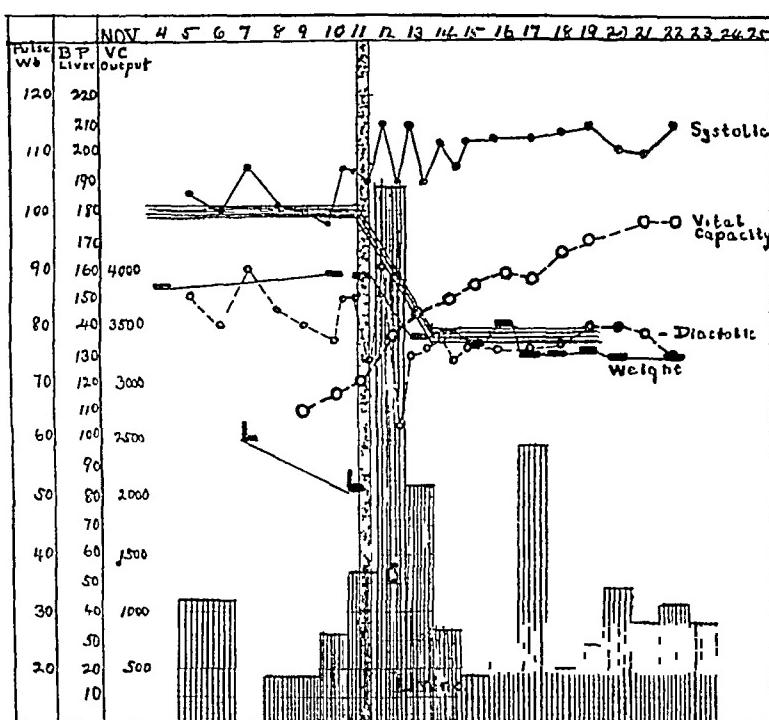


Fig. 4 (Case 1).—Diuresis, loss of weight, rapid decrease of liver, rise of vital capacity (sudden relief of symptoms).

Within forty-eight hours after the administration of digitalis the liver could still be felt by deep palpation, but instead of a visible mass in the upper abdominal quadrant there was a depression beneath the margins of the rib on both sides. The symptomatic improvement also was sudden and most impressive. He received 12 cc of the tincture at 9 a.m. That afternoon for the first time during the week of his stay in the hospital he had no dyspnea and no Cheyne-Stokes respiration. These symptoms did not return during his subsequent stay in the hospital. No more remarkable result from digitalis administration had ever come under our observation in any patient irrespective of whatever cardiac mechanism may have been present.

The thirteenth case, the graphic record of which is given in Figure 5, presents evidence which is most convincing of the effects of digitalis. It will be seen that during a period of nine days this patient improved under rest in bed. His weight decreased 10.4 kg., there was a decrease in the size of the liver, a rise in vital capacity and an improvement in symptoms. Following this, for a period of about a week, his condition was stationary, there was little decrease in the liver, no appreciable change in weight, no rise of vital capacity and no further symptomatic improvement. He was then given 21 c.c. of tincture of digitalis within twenty-four hours. There was a prompt diuresis, loss of weight (9.8

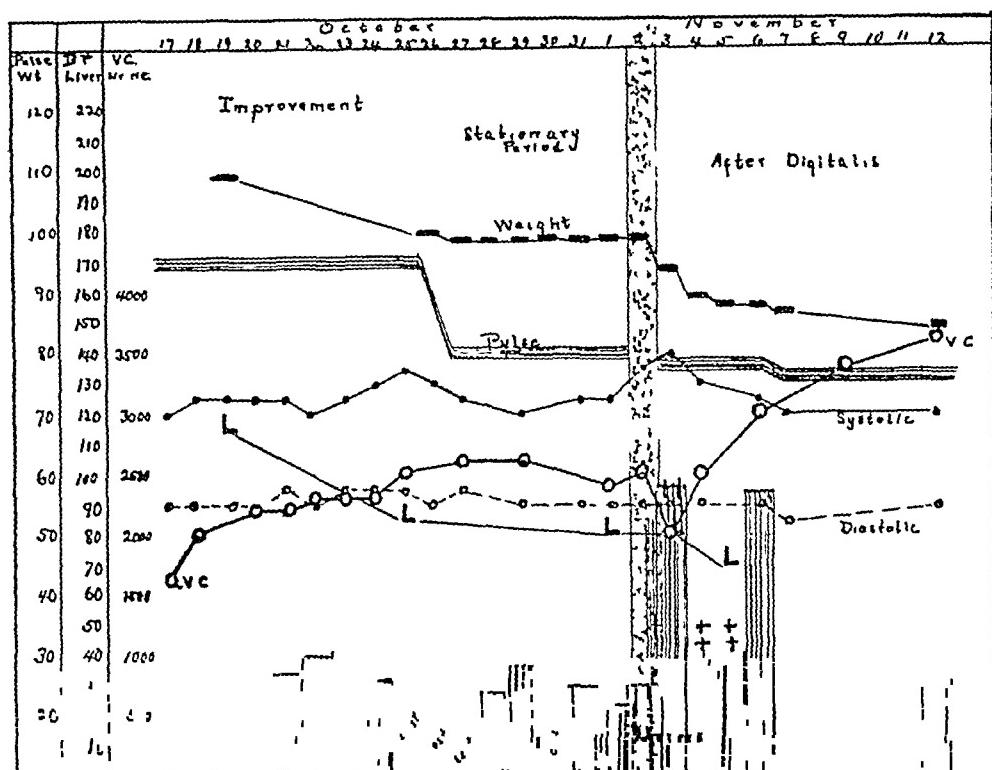


Fig. 5 (Case 13) — Improvement under rest, a succeeding stationary period and a further sudden effect from digitalis. Amounts of urine after digitalis are incomplete.

kg in forty-eight hours), rise of vital capacity and improvement in symptoms. Not all of the urine was collected, the incomplete data being indicated by the + marks in the figure.

The eighteenth case (Fig. 6) showed a relief from symptoms which was as sudden and remarkable as were the other effects that are recorded graphically. Because this case presented some unusual features and was, at the same time, most convincing of the strikingly beneficial effects of digitalis, a summary of the case is published, together with the chronological notes that were made in the history at the time of study.

A P., a colored man, aged 48, married, a Pullman porter, was admitted to the hospital on Feb 14, 1923, he was discharged on March 18, 1923, improved. The diagnosis was syphilis, myocarditis, chronic (syphilitic), hypertrophy of the heart, dilatation, chronic cardiac, cardiac decompensation, aortitis (syphilitic), general arteriosclerosis. The Wassermann test was four plus, repeated (same). There was no fever.

The patient's chief complaints were dyspnea, cough, edema and weakness. He had had a few attacks of sore throat twenty years before and an occasional winter cough for six or seven years, he had not had rheumatism. He had had gonorrhea ten years before and a primary sore twelve years before of two weeks' duration. He had suffered from weakness for three or four months, also a cough which had been worse for the past four weeks. He had had dyspnea for four weeks and a slight dyspnea four months before. Edema had been present for three weeks.

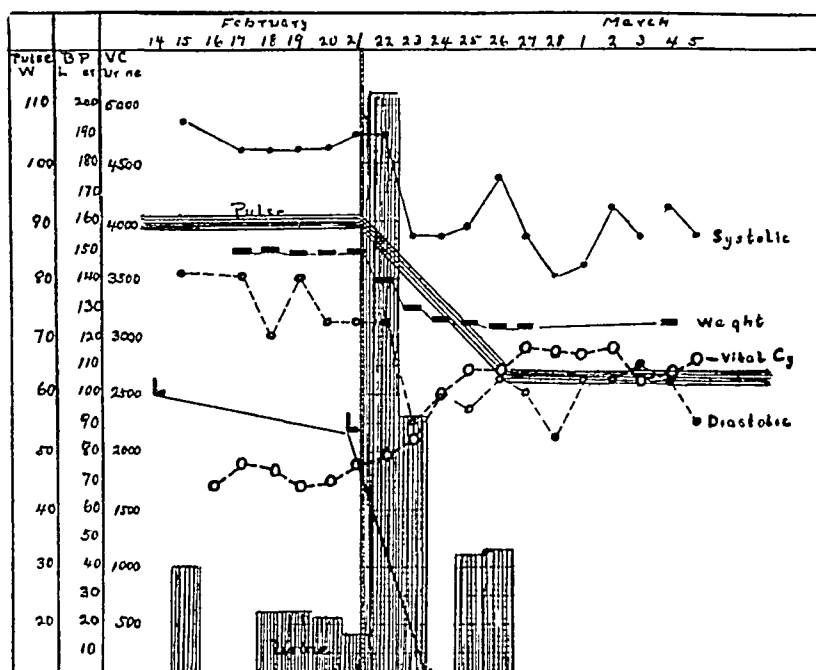


Fig 6 (Case 18) —Diuresis, loss of weight, shrinkage of liver, rise of vital capacity (sudden relief of symptoms)

Condition on Admission—When admitted to the hospital he had orthopnea and moderate edema. The liver extended 10 cm below the costal margin. There was a soft systolic murmur at the apex and over the precordium. There was dulness at the base of the right lung. The vital capacity was 1,700. The phenolsulphonephthalein excretion was 40 per cent. The blood pressure was systolic, 196, diastolic, 112. The maximum heart dulness was 14.5 cm in the sixth intercostal space, 2.5 cm to the right in the fourth space.

The urine contained 1.5 gm of albumin. There were finely granular and hyaline casts. The electrocardiogram showed "T" depressed in I, QRS, 0.1 of a second, P-R, 0.15 of a second. There was left ventricular preponderance. The nonprotein nitrogen content was 32.2 mg.

Treatment and Course—The patient was put to bed and given medium nephritic diet. Fluids were limited to 2,000 cc.

Feb 21, 1923 After seven days' observation the patient said his short breathing was "just the same". His cough was a little better. The pulse had

shown no tendency to fall—perhaps a tendency to rise a little. The blood pressure was about constant. The weight was constant. The vital capacity showed no tendency. The liver was fairly definite at 875 cm below the costal margin, a slight decrease. He had Cheyne-Stokes respiration. There was moderate edema of the legs and slight edema of the abdominal wall. The heart apex was in the sixth intercostal space, about 155 cm to the left, there was a long, low systolic murmur here, lower at the left sternal border. There was slight dulness at the right base and a few moist râles at both bases. There had been little, if any, improvement. Cheyne-Stokes respiration had developed. The patient had had no "doctor's medicine" during the past five weeks. Tincture of digitalis was ordered as follows (estimated dose would be 26 cc without allowance for edema) 10 cc at 8 p.m., 3 cc at 10 a.m., 3 cc at 1 p.m., total, 16 cc.

Feb 22, 1923, 9 30 a.m. Asked how he was, the patient said "sick." He was nauseated, but did not vomit. Asked how he felt, aside from nausea, he said "better," with emphasis. He said that he passed "five times as much urine" during the past night as during the previous night. He said he had not been "short of breath" during the past night for the first time since entrance. He had received 10 cc of tincture of digitalis at 8 p.m. on Feb 21, 1923. The output for the twelve hours was 2500 cc, his weight during the forenoon of February 21 was 186 pounds (84.5 kg), on the forenoon of February 22 he weighed 175½ pounds (79.6 kg). The liver was 825 cm below the costal margin (about the same as yesterday). The apex beat was regular 86, there was considerable visible edema.

The reaction to digitalis had been as remarkable as it usually is in cases of auricular fibrillation (A note to this effect was made thirteen and one-third hours after administration.) An electrocardiogram had not been made. The vital capacity was 1,975. The blood pressure was systolic, 185, diastolic, 125. The past night was the first of seven consecutive nights that the patient had not received morphin which was ordered to be given when necessary. Remainder of digitalis was to be omitted.

Feb 23, 1923, 9 a.m. The patient said he was nauseated, he had vomited a few times the preceding day. His respiration varied in intensity, but not rhythmically—there was no apnea. The abdominal and the chest walls were thinner. There was slight edema around the ankles and lower tibia. He had not slept well on account of pain in the upper part of the right side of the abdomen, but there had been no coughing or dyspnea. The liver was less easy to feel, apparently it was 6 cm below the costal margin, it had gone down. The apex beat was forceful in the fifth intercostal space—1325 cm to the left. There was a soft systolic murmur there, louder at the base. The patient said that he felt better except for the pain. He had a slight cough, but no dyspnea.

Feb 24 1923, 10 30 a.m. The patient was asleep. When awakened he said that he felt very well and that he had slept "very good." He had had little cough and no dyspnea since digitalis was administered. He had had no pain in the region of the liver since the previous day. The liver could not be felt, there was some resistance in the right upper quadrant. There was dulness about 1 cm below the costal margin, a remarkable decrease in two days. There was no edema or nausea.

Summary. There had been a rapid relief from symptoms (pain in the liver region for one day) and a loss of 22 pounds (10 kg) in two days. There had been diuresis, loss of edema, shrinkage of the liver, and a rise of vital capacity—200 cc in two days. There was a sudden drop of blood pressure on the second day (30 points). There was as complete and striking relief as in fibrillators, with no considerable reduction in the apex rate—not more than 10 beats a minute, if that many.

TABLE 2—Results in Condensed Form

Descriptive Data		Result												
No.	Diagnosis	Blood Pressure	Pulse	Edema	Fn	Wisell Large man Test	Hospital Result	Loss of Fluids	Loss of Weight	Diuretic resis-	Rise in Vitality	Improve-ment	Blood Pressure	
		(Yes) 1	(Yes) 1	Yes	Neg ¹ ative	Yes	Yes	Yes	Yes	Sympathoms	Lower	Rise	Fill	Remarks
1	Chronic myocarditis, decompensation	135/145	100	(Yes) 1	Yes	Neg ¹ ative	Yes	Yes	Yes	Yes	Yes	S (S)	D	Sudden relief
2	Aortic insufficiency, decompensation	120/ 30	100	(Yes) 1	Yes	4 plus	None	Yes ?	No	No	No	Yes	S (t)	
3	Chronic myocarditis chronic nephritis	130/ 85	90	Yes	Yes	Neg ¹ ative	No note	Yes	Yes	No	No	No	S (t)	Remarkable liver shrinkage
4	Chronic myocarditis, decompensation chronic nephritis	128/103	90	Yes	Yes	Neg ¹ ative	D ed	No	No	No	No	No	S (t)	Pulmonary thrombosis
5	Aortic insufficiency, decompensation	145/ 65	92	Yes	Yes	4 plus	Died	No	No	No	No	No	D (t)	
6	Aortic insufficiency, chronic myocarditis, decompensation	165/ 87	80	(Yes) 1	Yes	Neg ¹ ative	Improved	None	No	No	No	No	No (2)	
7	Chronic valvular disease, stenosis and insufficiency, decompensation	95/ 80	120	Yes	Yes	Neg ¹ ative	Improved	Yes	?	?	Yes	Yes	No	Auricular fibrillation after subacute digitalitis
8	Aortic insufficiency decompensation	120/ 70	78	(Yes) 1	(No) 3	Neg ¹ ative	Improved	None	Yes	No	(?) ³	No	S (t)	Toxic improvement with rest
9	Chronic myocarditis, chronic nephritis, decompensation	215/130	80	Yes	Yes	Neg ¹ ative	Died	No	Yes	Yes	Yes ?	No	S (t)	Toxic rhythm improvedelayed
10	Chronic myocarditis, mural thrombi, decompensation	158/100	80	(Yes) 1	Yes	Neg ¹ ative	Died	None	Yes	Yes	Yes	No	D (t)	Improvement with no rise in vitalicity
11	Emphysema, chronic bronchitis	118/ 80	85	No	Yes	Neg ¹ ative	Improved	None	Yes	No	No	No	S (S)	Not a cardiac case
12	Chronic nephritis, chronic myocarditis	210/108	85	No	Yes	Neg ¹ ative	Improved	None	No	No	No	No	D (S)	Not decompensated
13	Chronic myocarditis, chronic nephritis, decompensation	125/ 90	80	Yes	Yes	Neg ¹ ative	Improved	Yes	Yes	Yes ?	Yes	No	S (t)	A, improvement with rest, B stationary period with dug lus toxic, mixed result
14	Chronic myocarditis, chronic nephritis, decompensation	125/105	95	Yes	?	Neg ¹ ative	Improved	Yes	Yes	No	No	No	S (S)	
15	Chronic myocarditis, chronic nephritis, decompensation	215/135	102	No	Yes	Neg ¹ ative	Improved	None	Yes	Yes	Yes	Yes	S (S)	Duresis loss of weight, no visible edema
16	Chronic nephritis, small granular kidneys, arteroma coronary	185/135	86	No	No	Neg ¹ ative	Died	None	No	No	(?)	No	S (t)	Average result
17	Chronic myocarditis, aortic, decompen-sation	140/ 70	86	"No" 2	Yes	3 plus	Improved	"Yes"	Yes	Yes	Yes	Yes	No chal e	Not a cardiac case
18	Chronic myocarditis, aortic, decom-pensation	188/130	90	Yes	Yes	4 plus	Improved	Yes	Yes	Yes	Yes	Yes	S (S)	Sudden remarkable effect
19	Chronic myocarditis chronic nephritis decompensation	138/110	80	Yes	Yes	Neg ¹ ative	Improved	Yes	Yes	Yes	Yes	No (2)	D (t)	Average result
20	Chronic myocarditis chronic nephritis decompensation	195/ 90	68	Yes	Yes	Neg ¹ ative	Improved	Yes	Yes	Yes	No	Yes	S (t)	Average result

Indicates that clinical observation was favorable, but measurements decreased after digitalis therapy, pulse was higher than before, but visible column.

Indicates that clinical observation was favorable, but measurements decreased after digitalis therapy, pulse was higher than before, but visible column.

Feb 25, 1923 The patient was quite comfortable and did not complain. The liver was not felt, there was dulness about 2 cm below the costal margin. There was a soft systolic murmur at the apex and base of the heart.

March 2, 1923 The patient had been allowed to sit up a few minutes each day. Twenty minimis of tincture of digitalis once daily was ordered.

March 16, 1923 There was a heaving impulse at the apex in the fifth intercostal space below and outside of the nipple, and a soft blowing systolic murmur. At the aortic area there was a definite, fairly loud, not prolonged diastolic murmur, occurring immediately after the second sound. There was also a soft systolic murmur in the aortic area. The systolic murmur was a little louder at the left sternal border but no diastolic murmur was heard there. The edge of the liver descended from beneath the costal margin on deep inspiration. No edema was present.

In order to obtain some notion of the constancy of these results and to determine as far as possible, in what class of cases they occur, a second table was constructed (Table 2). It is a summary of Table 1. It furnishes a brief description of each patient, giving the diagnosis, mean blood pressure, mean pulse rate, findings concerning edema and enlargement of the liver, the Wassermann reaction and the hospital result. Under "Result" is recorded whether or not, as a result of digitalis administration, there was a loss of edema, loss of weight, diuresis, diminution in the size of the liver, rise of vital capacity, improvement of symptoms, lowered pulse rate and rise or fall of blood pressure. The answers to these questions are derived not from impression but from the quantitative data recorded in Table 1. The cases are arranged in the same order in the two tables.

The foregoing charts and tables show that in certain cases there was a prompt diuresis (with loss of weight, loss of edema and decrease in the size of the liver) as a result of digitalis administration in large dosage. Improvement in symptoms was often sudden and impressive. In many cases there were changes in pulse rate and in blood pressure.

TYPE OF PATIENTS AFFECTED

In order to throw some light on the question of the classes of patients with normal rhythm that are improved by the administration of digitalis, cases with similar findings were arranged in groups, and notation was made as to how many of each group were improved and how many not improved.

Table 3 shows that of ten patients with "chronic myocarditis" who showed edema and signs of cardiac decompensation without aortic disease and with negative Wassermann reactions, nine were improved, one not improved. Two patients with chronic nephritis, four with aortic insufficiency and edema, and one with chronic bronchitis and emphysema showed little evidence of improvement from digitalis. Two patients with myocarditis who were probably syphilitic, and one patient with mitral disease, all of whom gave evidences of decompensation, were improved by the drug.

This question was approached in still another way. A table was made which divides the cases into two groups, those who were "Improved" and those who were "Not Improved" (Table 4).

It is at once apparent from a glance at this table that the type of patient who was improved by digitalis belongs in the category of those with "chronic myocarditis," or, to employ a term that is becoming more generally used, "myocardial insufficiency," such patients exhibiting dyspnea on exertion, an enlarged and dilated heart usually with a systolic murmur at the apex, enlarged liver and edema. The hospital

TABLE 3—*Cases Arranged in Groups with Results in Each Group*

Group	Case Number	Result	
		Improvement	No Improvement
I Chronic myocarditis	1, 3	1, 3	
No suspicion of syphilis	4, 9	9	
No aortic disease	10, 13	10, 13	4
Decompensated	14 (15)	14, 15	
Edema when admitted	19, 20	19, 20	
Total number	ten	nine	one
II Chronic nephritis no edema	12, 16		12, 16
Total number	two		two
III Aortic insufficiency	2, 5		2, 5
Decompensated	6, 8		6, 8
Edema when admitted	four		four
Total number			
IV Mitral disease, edema, decompensated	7	7	
Total number	one	one	
V Emphysema and chronic bronchitis no edema, not decompensated	11		11
Total number	one		one
VI Myocarditis, probably syphilitic decom pensated	17, 18	17, 18	
Total number	two	two	

diagnosis in Case 7 was "valvular disease, chronic cardiac, mitral stenosis and insufficiency." The patient presented, however, in addition to the usual evidences of mitral disease, the characteristic features above mentioned.

The patients in Cases 1 and 10 had had edema, but it had disappeared during the observation period. Both doubtless still had excess tissue fluid, however, for after digitalis administration both lost weight and had diuresis. The face of one (Case 1) was noticeably much thinner in appearance after administration of the drug.

The patient in Case 15 had no apparent edema. Notwithstanding this, he lost 27 kg in weight in two days after receiving digitalis. Unfortunately, his rate of loss (if any) before digitalis was not observed. His urine output for the first twelve hours after administra-

TABLE 4.—Comparing Cases that were "Improved" and Cases that were "Worse."

¹ indicates that edema had disappeared, coronary effect, beneficial effects delayed

tion of digitalis was 1,500 c.c. It seems probable that he had excess fluid in the tissues which was not extensive enough to cause pitting on pressure.

The patient in Case 17 showed no pitting. The ankle measurements, nevertheless, increased a little during the observation period, and her weight increased slightly, while following digitalis administration the ankle measurements decreased, and she lost weight.

If the patients in Cases 15 and 17, then, be regarded as having had edema when admitted to the hospital, it may be stated that all of the twelve patients who were improved by administration of digitalis showed evidence of cardiac decompensation with edema of greater or less extent. They belonged, with the exception of Case 7, to the group that is usually called "myocardial insufficiency."

Of the eight patients who were "not improved," those in Cases 11 and 16 did not have cardiac disease, while nephritis appeared to be responsible for the symptoms in Case 12. Four had aortic disease. The remaining patient that showed no improvement (Case 4) belonged in the same category as those who showed improvement, that is, myocardial insufficiency. His condition, however, was grave on admission. His vital capacity at no time was higher than 1,230 c.c. He had, moreover, evidences of pulmonary thrombosis at the time of digitalis administration, and he died seven weeks later.

The patients with aortic insufficiency were not improved. The conclusion that no such cases may be benefited by digitalis, however, is not warranted from the study of such a small number of cases. The patient in Case 8 improved rapidly under rest. Had he received digitalis before the disappearance of the edema and before his improvement, these results might have been more rapid. He exhibited, moreover, a toxic rhythm and other evidences of toxic effect which may have prevented favorable action. There is little positive evidence, however, from these four cases, that digitalis is of value in cases of aortic insufficiency. Case 18 is of much interest in this connection. This case record, given above, shows that it was only about three weeks after digitalis administration that signs of aortic disease were noted. There was at that time a diastolic murmur at the aortic area. There were, however, no other evidences of aortic insufficiency. It would seem probable that the symptoms were due chiefly to syphilitic myocarditis, and that the aortic involvement was early.

MECHANISM OF ACTION

There remains for consideration the question of the mechanism by which digitalis (in large dosage) produces diuresis, disappearance of edema, decrease in size of the liver and improvement of symptoms in cases of myocardial insufficiency. The results in cases of this type have

been so uniform when large amounts of the drug have been given in a short time interval, whereas previous results from smaller dosage had been without benefit, that the question arises whether the rapid disappearance of edema is not a result of some physical or chemical reaction on the body fluids rather than of an effect on the heart or kidneys. When the subject of edema is better understood, the solution of this question will be nearer.

Certain observations in this study, however, offer strong evidence that the beneficial effects that followed the administration of digitalis to the patients with myocardial insufficiency were the result of some sort of action of the drug on the heart. This explanation is indicated by the rapid diminution in size of the liver, and is further supported by a study of a patient who showed toxic effects of rather high degree after digitalis administration.

This patient (Case 9 in Table 1) had received a massive dose of digitalis with strikingly favorable results about nine months previously (Case 1 in Table 1). On his last admission, after eight days' observation, he received tincture of digitalis as follows at 5 p.m., August 29, 5 cc, at 10 a.m., August 30, 5 cc, at 1 p.m., 5 cc, and at 6 p.m., 2 5 cc. Before receiving the last dose he vomited and felt worse than he had felt for some days. Following the last dose he was uncomfortable and had almost constant nausea. The next day, August 31, his blood pressure had fallen from systolic 200, diastolic 130, to systolic 140, diastolic 100. He looked much worse. Electrocardiograms showed nodal rhythm (transient) after the second dose (August 30), and a-v dissociation with an auricular rate of 131 and ventricular rate of 162 on August 31 (Fig. 7). During the succeeding days electrocardiograms showed abnormal rhythms and a gradual return to normal on September 8.

Figure 10 shows that there was a diuresis which increased in amount during the time that the toxic effects were wearing off his heart and which reached a maximum on September 8, the day his heart rhythm became normal. Edema had disappeared by September 9. This case will be reported more in detail, together with other toxic rhythms resulting from digitalis, in a subsequent paper. The important point for present consideration is that there was an early decrease in the size of the liver, which occurred before the full amount of digitalis had been received, that there was a toxic action on his heart, and that during the time when this was of high degree he had no diuresis, but that he began to have diuresis as his heart recovered, and that there was extreme diuresis which was delayed only so long as his heart showed the toxic effects of the drug. It is difficult to escape the conclusion that this diuresis with loss of weight and of edema was due to the action of digitalis, and that its delay was due to the lowered efficiency of his

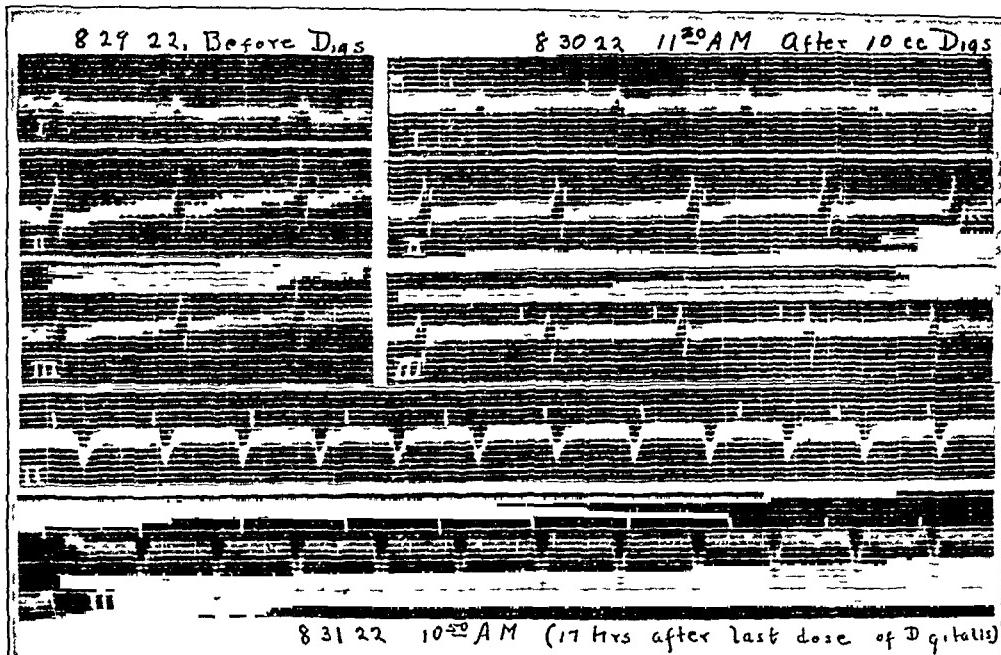


Fig 7.—Electrocardiograms of Case 9. The first shows the three leads before digitalis was started. The second shows nodal rhythm in Lead II. The third shows a-v dissociation with auricular and ventricular tachycardia of different rates. Note the change in complexes. The position of the "P" waves is indicated by markers.

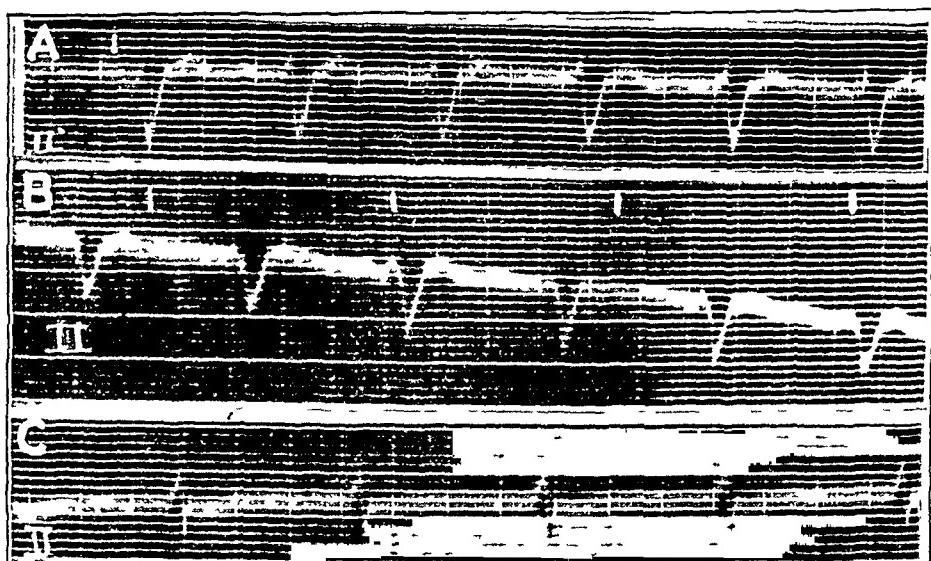


Fig 8.—Electrocardiograms of Case 9, Lead II. The first shows nodal rhythm, the second, a-v dissociation with slower auricular rate, the third, complex of same type as before digitalis, but still a-v dissociation. The Lead A was made on Sept 1, 1922, at 11 a m, that in B on Sept 1, 1922, at 3 p m, that in C on Sept 4, 1922.

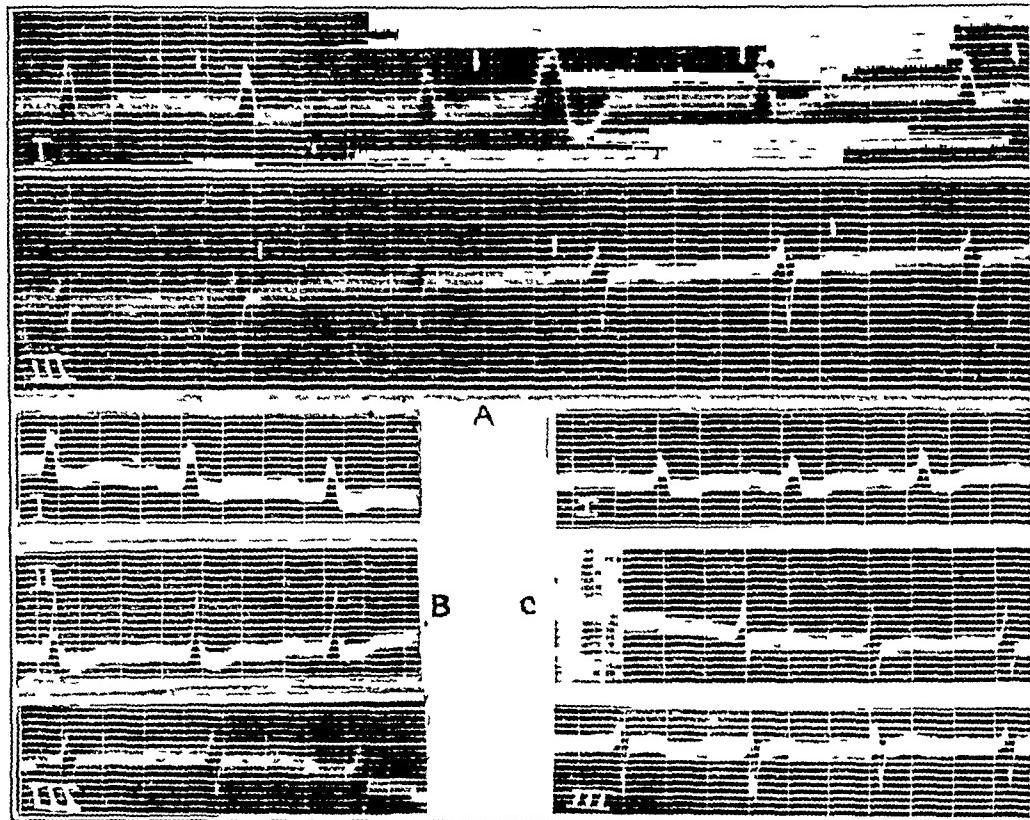


Fig 9.—Electrocardiograms of Case 9. The first shows complete heart block. The others show normal mechanism. The leads in A were made on Sept 7, 1922, those in B on Sept 8, 1922, those in C on Sept 9, 1922.

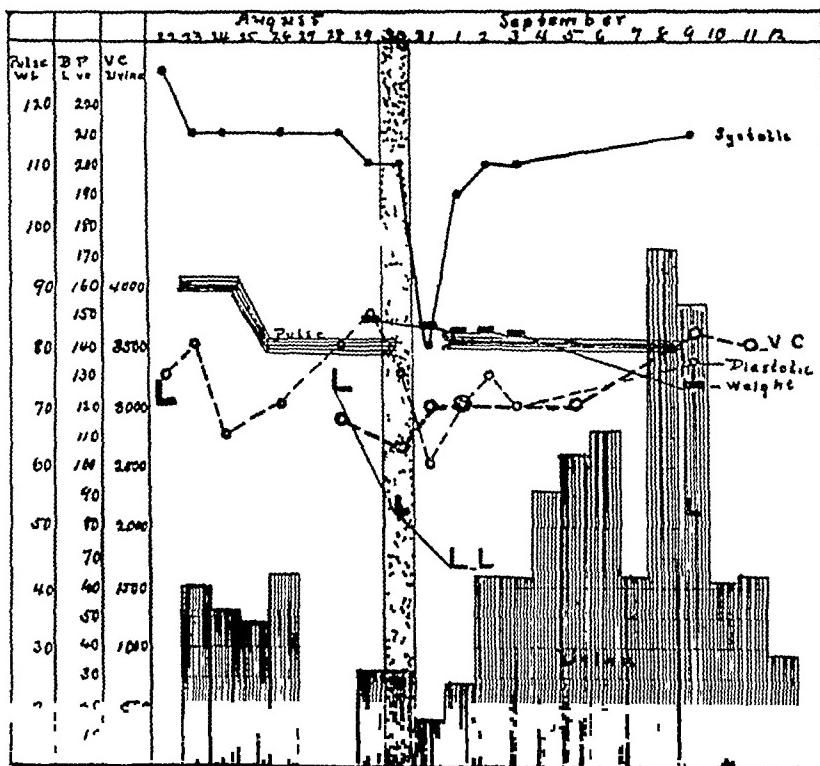


Fig 10 (Case 9).—Toxic effect, delayed diuresis and loss of weight.

heart while that organ was suffering the extremely toxic effects of the drug. In other words, the evidence is that digitalis acted directly on the heart and in some way increased its efficiency after the (temporary) ill effects had disappeared.

It has long been known that there is an action of the drug on the heart besides its effect on the conducting tissues between auricle and ventricle. The questions have been (1) Just what is this action? (2) Is it beneficial or not?

In this series, about thirty patients with myocardial insufficiency showed, with great uniformity, diuresis and symptomatic improvement after rapid digitalization. This fact per se does not prove that these beneficial results were due to a cardiac action of the drug. But we know that the drug has a cardiac action, and in one case that was carefully followed the beneficial effects did not appear until evidences of harmful effect on the heart had disappeared. There must be, then, some action of digitalis, besides its effect on the conducting tissues, by virtue of which it increases cardiac efficiency in these cases. What is this action? This question has been the subject of many careful experimental studies, and further comment here could add nothing toward its solution.

It should be stated, however, that this beneficial action appears to be independent of any slowing in ventricular rate in cases with normal mechanism. There is still much confusion on this subject of slowing. Eggleston,⁵ in 1915, regarded slowing as an evidence of the effect of digitalis on cases with normal mechanism. In 1920, he says¹⁰ that it "generally produces considerable slowing" in "those cases of heart failure in which marked oedema is present" but that with this and one other exception "the therapeutic administration of digitalis is seldom followed by a significant degree of slowing of the heart rate in the presence of the normal sinus rhythm." With the latter part of this statement most careful observers are now in agreement, although one not infrequently meets practitioners who still expect slowing from digitalis administration to patients with sinus rhythm.

Our observations indicate that even in patients with marked edema whose mechanism in normal slowing is not a characteristic attendant on improvement, and that even when it occurs it follows the diuresis and is a result rather than a cause of the improvement. The patients in this series whose heart rate previous to digitalis administration was fast (above 80) quite commonly showed a decline in rate to about 80 after improvement. Those who were improved by the drug but had had a slow rate before its administration, showed no further slowing with improvement (Table 1, column showing mean pulse rate, also

¹⁰ Eggleston, Cary. Some Newer Concepts in Digitalis Therapy, Am J M Sc **160** 625 (Nov) 1920

Figures 2, 3 and 4) The improvement in Case 10 (Fig 3) was clearly not associated with a change in rate. The rate had declined spontaneously until the day before digitalis administration, but showed no fall with his sudden improvement at that time. The patient in Case 13 (Fig 5) showed a much greater spontaneous drop in rate following improvement with rest than he showed at the time of his pronounced improvement from digitalis. In the former instance, his rate declined from 95 to 80, while at the time of digitalis administration (and marked diuresis) there was a further reduction in rate to only 78. Case 18 (Fig 6) showed a considerable fall in rate subsequent to, rather than at the time of, sudden improvement (see note of February 24). Case 20 (Table 1) showed a well marked result from digitalis. The patient's mean heart rate, however, was only 68 before the administration of the drug, but was showing an upward trend. This upward tendency continued, and the mean rate after digitalis was 72—a normal rate.

Slight spontaneous changes in rate were common in all these cases, and were as frequent among those who were not improved as among those patients that showed diuresis and symptomatic improvement. It would seem clearly indicated, therefore, that slowing is not an integral factor in the improvement in these cases, and that when it does occur it is rather a subsequent readjustment to improved conditions of the circulation, which would take place after marked improvement from any cause.

BLOOD PRESSURE

There was no uniform effect on blood pressure. By far the commonest result was a temporary rise of systolic pressure (Table 2). Quite frequently the diastolic pressure also was raised, and the tendency appeared to be for this diastolic rise also to be temporary. In a few instances the elevation of both was sustained. In one patient who showed a greatly beneficial effect from the drug (Case 1, Fig 4) there was a sustained rise of systolic pressure, with a sustained fall of the diastolic. Another patient whose improvement was most impressive (Case 18) showed a delayed fall of both the systolic and diastolic readings, which were sustained.

The rise of systolic pressure that usually occurred was never great. There appeared to be no relationship between the original level of pressure and its course after digitalis. Whether or not the patient was improved by the drug appeared to bear no relationship to the change in blood pressure.

CONCLUSIONS

1 Tincture of digitalis, when given by mouth in large doses over a short time interval, affects favorably certain patients with normal heart rhythm.

2 The favorable effects are improvement in symptoms, diuresis, loss of edema and decrease in size of liver

3 The patients in whom these effects occur with most consistency belong to the class known as "myocardial insufficiency"

4 The improvement from digitalis in these cases does not depend on change in ventricular rate

5 This improvement is probably due to increased muscular efficiency brought about by the action of the drug on the heart muscle

6 Patients with myocardial insufficiency improve under proper digitalis administration in about the same proportion of cases as do patients with auricular fibrillation. The improvement in the former class of cases is usually, perhaps, of somewhat less extent, but it is frequently as impressive as the most striking results that occur in patients with fibrillation of the auricles

7 It should be stated here that certain manifestations of toxic action, which will be reported in greater detail, were observed with sufficient frequency to indicate that the method of rapid digitalization that was employed in this study is not without danger. The dosage used was doubtless, in many cases, above the optimum amount.

721 University Club Building

BOOK REVIEWS

LA DÉGÉNÉRESCENCE HÉPATO-LENTICULAIRE Maladie de Wilson Pseudo-Sclerose Par H C Hall, Ancien Chef de clinique a l' "Hôpital de Bispebjerg," Copenhague Creface du Professeur Pierre Marie Paper Price, 20 francs, net Pp 361, with 44 illustrations Paris Masson et Cie, 1921

This is the most complete monograph on the subject of lenticular degeneration that has yet appeared Hall first gives a brief review of Wilson's four cases and a summary of the clinical features of the syndrome called by Wilson "progressive lenticular degeneration" He then correlates the Westphal-Strumpell pseudosclerosis with Wilson's syndrome, he believes that the corneal pigmentation noted in many cases of pseudosclerosis is of frequent occurrence in progressive lenticular degeneration, although it was overlooked by Wilson He next reports four cases of his own and the histories of three other patients provided by the courtesy of his confreres in Copenhagen Four of these patients belonged to one family, and two others were brothers In the review of these seven cases he expresses his opinion that one case was an example of true Wilson's disease, that Cases 2 and 3 were pseudosclerosis, and that Cases 4 to 7 form a familial group of a nervous disease resembling Wilson's syndrome, with hypertonia as the most intensive symptom We feel that the data supplied by Hall for the last group are too incomplete to warrant this assumption

The author next tabulates the sixty-eight cases in the literature of Wilson's disease and pseudosclerosis of the patients, fifty were males and eighteen females The duration of the twenty-two fatal cases varied from two to seven years Corneal pigmentation was only looked for in thirty-seven cases and was found to be present in twenty-one, or more than 50 per cent, of these thirty-seven cases, only nine were Wilson's disease, and in three of them (those of Pollock, Soederbergh, Hall, Case 1) corneal pigmentation was observed Hall, therefore believes that the corneal pigmentation is pathognomonic of both Wilson's disease and pseudosclerosis, and not merely of the latter syndrome

Speech is variously affected, the condition ranging from mere dysarthria to complete anarthria Involuntary movements and hypertonia are common symptoms besides these, contractures, associated movements, ataxia, adiado-kinesis, epileptiform and apoplectiform crises are observed While the tendon reflexes are usually normal, Babinski's phenomenon was noted in twelve cases

While the deep and superficial sensation is intact, the gait is affected and of a peculiar character due to the hypertonia and tremors The electrical reactions are normal The mental state is more or less affected The cerebro-spinal fluid was normal except in two cases, in which a slight pleocytosis existed The liver may be found decreased and the spleen increased in size Alimentary levulosuria has been demonstrated in four cases, urobilinuria is not constant, however Glycosuria was present in six cases The skin may show pigmentation, as was noted in six cases Postmortem a nodular cirrhosis was an absolutely constant feature both in true Wilson's disease and pseudosclerosis So far as the anatomic alterations in the nervous system are concerned, Stoecker and Hall have found all transitions between the picture described by Wilson in his progressive lenticular degeneration and those described by Alzheimer in the Westphal-Strumpell pseudosclerosis Hall, therefore, suggests a common name for the two syndromes, namely, "hepatolenticular degeneration" These cases belong to the heredofamilial nervous diseases which enter into the Gowers concept of abiotropic affections

MODERN ASPECTS OF THE CIRCULATION IN HEALTH AND DISEASE By CARL J WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University Second edition Thoroughly revised Price \$7.50 Pp 661, with 204 engravings Philadelphia and New York Lea & Febiger, 1923

In the present work, the first edition which was favorably received eight years ago has been thoroughly revised. The chapters have been extended and much valuable material has been added in the new ones on "The Efficiency and Adaptability of the Heart," "Vascular Control of the Circulation," "The Principles and Practice in Optical Registration of Mechanical Pulsations in Man" and "The Dynamic Consequences of Chronic Heart Disease." The general plan of the original edition has been retained. The book is divided into three sections. The first deals with the physiology of the circulation, the second with graphic methods for the clinician and the third with disease of the heart and circulation.

The physician is constantly becoming more aware of the importance of a thorough basic knowledge of physiology in the interpretation of clinical problems. The applications of physiologic methods in recent years have been chiefly responsible for the rapid advancement in our knowledge of the heart. The author of the present work is one of the foremost authorities on the physiology of the circulation. He has personally investigated many phases of the subject and is thoroughly familiar with the entire field. Those interested in the cardiovascular system will greatly appreciate Dr. Wiggler's second edition. The clinician may raise the objection that some of the subjects are considered briefly in the section on disease of the heart and circulation. In this connection it may be added that this section was evidently not intended to be an exhaustive consideration of the subject, as might be implied by the subject, but to correlate so far as possible the normal and pathologic physiology. In this respect, the author has satisfactorily accomplished his aim.

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STUDIES ON THE VISCERAL NERVOUS SYSTEM

ON THE REFLEX CONTROL OF THE PYLORUS¹

A J CARLSON, PH.D., AND S LITT, M.S.
CHICAGO

It occurred to us that the device used in the study of the reflex control of the cardia and lower esophagus¹ might be adapted to a similar study of the pylorus, and, for acute experiments on anesthetized animals, might possibly present less local trauma, irritation and abnormal conditions than were involved in previous work on the pylorus, excepting the use of the roentgen ray on man and animals not under anesthesia.

The mechanism of pylorus control has challenged numerous investigators in recent years, partly from physiologic interest, partly because of the importance of the pylorus in the motor and secretory disturbances of the stomach. As regards local mechanism involving only the pylorus and adjacent regions of the antrum and upper duodenum, Cannon,² in 1904, summarized his own observations and those of previous investigators in his theory of "acid control of the pylorus," that is, the acid of the gastric juice acting on the stomach side of the pylorus opens the pylorus, while acid on the duodenal side closes the pylorus, both actions being primarily local reflexes. The part of the theory stating that acid, acting on the stomach side, opens the pylorus, has not been substantiated by subsequent investigations, largely by methods different from Cannon's. Thus Morse reports that water leaves the stomach faster than acid, and weak acids leave the stomach faster than strong acids. Cowie and Lyon,³ working on infants, found that rendering the food either acid or alkaline delays gastric evacuation. They also maintain that free acid in the stomach is not necessary for pyloric relaxation and initial gastric evacuation. Spencer⁴ and others, working on adult persons, reach essentially the same conclusions and report specifically that rendering the food alkaline hastens the emptying of the stomach. McClure⁵ and others, working with the roentgen ray on adult persons, report that a mixed, well masticated meal starts to pass through the

* From the Hull Physiological Laboratory of the University of Chicago

1 Carlson, Boyd and Pearcy Am J Physiol 61 14, 1922

2 Cannon Mechanical Factors of Digestion, 1911, p 96

3 Cowie, D M, and Lyon, W Further Observations of the Acid Control of the Pylorus in Infants, Am J Dis Child 2 252 (Oct) 1911

4 Spencer Am J Physiol 39 459, 1916

5 McClure, C W, Reynolds, L, and Schwartz, C O On Behavior of Pyloric Sphincter in Normal Man, Arch Int Med 26 410 (Oct) 1920

pylorus a few minutes after eating begins, and that introducing acids in the duodenum does not essentially modify the rate of the evacuation Luckhardt and Carlson⁶ found (in man, and dog) that opening of the pylorus and the passing of the gastric contents into the duodenum was correlated with the periodic tonus rhythm of the stomach rather than with the variations in gastric acidity

It needs scarcely be pointed out that the rate of evacuation of the stomach cannot be used as a direct measure of pylorus tonus, because, except in cases of pathologic pylorospasm or mechanical narrowing of the pyloric orifice, the emptying rate of the stomach depends on the motility of the stomach and the reflex state of the duodenum, as well as on the tonus of the pylorus. On the other hand, most observers agree that mechanical or chemical irritation of the duodenal mucosa induces spasms of the duodenum, regurgitation of duodenal contents into the stomach and pyloric contraction or spasm of varying duration.

The control of the pylorus by extrinsic reflex mechanism involves first of all a consideration of the path and character of the effluent nerves of this region. There are some seeming contradictions between the individual reports on this phase. The literature is reviewed in the recent paper by Thomas and Wheelon⁷.

Thomas and Wheelon, working on the anesthetized dog, introduced a specially constructed enterograph into the antrum, pylorus and upper duodenum. This apparatus consisted of three separate chambers in a solid rubber case, the chambers being covered with thin rubber. The apparatus was adjusted so as to give separate records of the antrum, pyloric and duodenal contractions. By means of this device they report rhythmic contractions of the pylorus (from three to five per minute) contraction and inhibition of the pylorus on stimulation of the peripheral ends of both the vagus and the splanchnic nerves, but only an inhibitory action on the pylorus by epinephrin. They conclude that the vagi as well as the splanchnic nerves carry motor and inhibitory fibers to the pyloric sphincter.

The enterograph of Thomas and Wheelon is straight and in the transverse diameter unyielding or rigid at four points. The apparatus was fixed in place by sutures through the antrum. It would seem that the rigidity of the apparatus introduces serious abnormal conditions and local irritations, especially when there is marked tonus and contractions of regions about the apparatus.

Few studies appear to have been made on the extrinsic reflex control of the pylorus. Barber and Stewart,⁸ in a preliminary note, have described a diffuse pylorospasm in dogs, with a fundic relaxation fol-

6 Luckhardt, Phillips and Carlson Am J Physiol 50 57, 1919

7 Thomas and Wheelon J Lab & Clin Med 7 3, 1922

8 Barber and Stewart Proc Soc Exper Biol & Med 17 155, 1920

lowing irritation of the gallbladder, the appendix and the duodenum. They report that this pylorospasm disappears on irritation of the parietal peritoneum. The method of recording or observing these reflexes into the pylorus are not described.

METHODS

The experimental arrangements are shown by the diagram in Figure 1. The pyloric condom balloon (*C*) with the retention plug (*D*) may, for the sake of brevity, be called a "pylorometer." For construction and size of this contrivance the reader is referred to our report on innervation and reflex control of the cardia.¹ It is obvious that if the tonus of the cardia exceeds the air pressure in the tube system *E*, the portion of the delicate balloon (*C*) in the pyloric region will remain collapsed, and manometer *A* will record no pressure variations in the

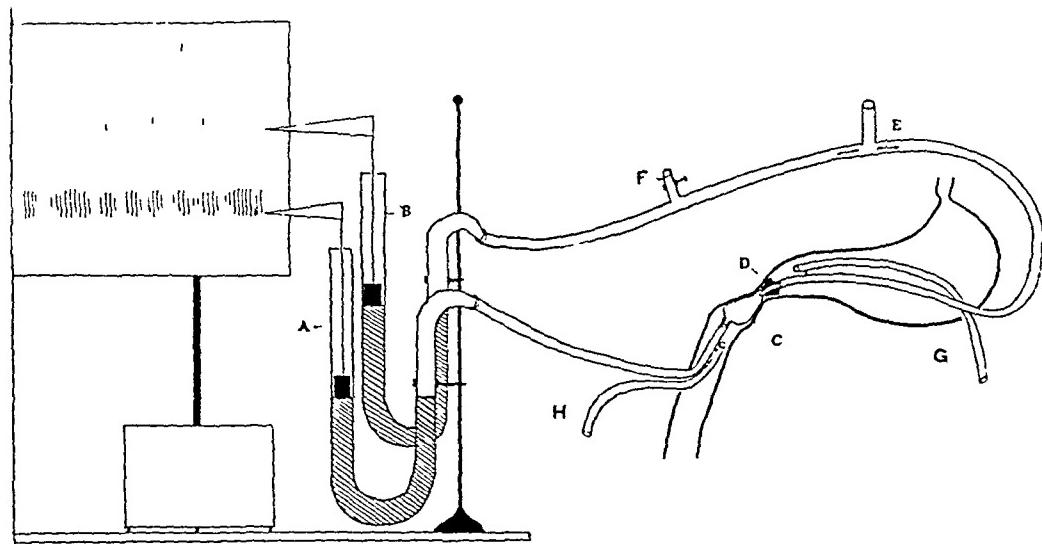


Fig 1.—Arrangement of contrivances for continuous study of the tonus and contractions of the pylorus in experiments on dogs. *A*, water manometer connecting with the balloon in the pylorus (*C*), and recording the tonus of the pylorus; *B*, control water manometer in the circuit recording possible variations in rate and force of the periodic insufflation of tube *E* with air; *C*, condom balloon in pylorus and upper end of duodenum; *D*, retention plug of the balloon anchored on the antrum side of the pylorus; *E*, rubber tube connecting with a motor driven bellows that provides periodic insufflation of the tube system and pyloric balloon; *F*, outlet tube controlling the degree of the periodic air pressure in the system furnished by the motor driven bellows; *G*, tube serving to introduce fluids into the antrum pylori; *H*, tube serving to introduce fluids into the duodenum.

tube system *E*. The pylorometer was introduced through an opening in the fundus, and anchored in place by the rubber tube attached to the pyloric end of the balloon and by a linen thread attached to the retention plug. Tube and thread were carried out of the duodenum by a small slit in the wall from 8 to 10 cm below the pylorus. In a few cases the gastrostomy and the duodenostomy were made aseptically two

days before the experiment. In every case from one to one and one-half hours were allowed to elapse after fixing the pylorometer in place and beginning the observation, to eliminate so far as possible abnormal states due to the trauma and mechanical irritation incident to adjusting and recording devices.

Periodic variations in air pressure in the tube system (*E*) were secured by motor driven bellows, with adjustable rate, and volume output. The maximum pressure in the system was further regulated by the size of the aperture, *F*. Manometer *B* served as a control on any accidental variations in the rate and amplitude of air pressure variations in the tube system. Unless the pylorus is extremely atonic, the balloon (*C*) part on the duodenal side of the pylorus does not completely collapse between the positive pressure periods in the tube system. The amount of permanent positive pressure in the manometer *A* is thus a measure of degree of pylorus tonus. The float in the control manometer (*B*) always returns to *O* pressure, owing to the open exit for the air of *F*. But the spasm of the pylorus may be so great that no air can enter the balloon and tube system beyond the pylorus. In this state the method permits the recording of pyloric relaxation only.

The position of the pylorometer was always verified at the end of each experiment.

All the experiments were made on dogs, using barbital anesthesia, or barbital with a trace of ether. In a few experiments ether was used exclusively. Care was taken to keep up the normal body temperature. The dogs were not fed for twenty-four hours prior to experimentation, so as to insure an empty stomach.

For the observations on local reflexes the water, acids and alkalies (at body temperature) were introduced through the rubber tubes, *G* and *H*. These tubes were tied to the pylorometer tube system in the stomach and duodenum so as to insure the contact of the fluid in the pyloric antrum and within a few centimeters of the pylorus on the duodenal side.

RESULTS

1. *Spontaneous Rhythm of the Pylorus*.—Under the conditions of our experiments, the spontaneous motor behavior of the pylorus varied greatly in different animals, and from time to time in the same animal, when observations were continued for from four to six hours. In some cases, the pylorus was in a state of extreme spasm lasting for hours; in other cases, it was completely relaxed and quiescent, but usually the pylorus was in moderate tonus, with periodic variations of tonus. This tonus rhythm may run regularly for hours at a rate of from three to four waves a minute, or the tonus waves may appear more like spasms, the contraction phase lasting for from one to several minutes, with correspondingly long relaxation phases. The regular

and irregular tonus rhythm of the pylorus was also noted by Thomas and Wheelon. Types of the pylorus rhythm as recorded by the present method are shown in Figure 2.

2. Influence of the Vagi Efferent Fibers on the Pylorus.—The acute or immediate effects on the pylorus of section of the vagi in the neck or of tetanization of the peripheral end of the cut vagi are variable, but depend in part on the state or condition of the pylorus. The following results may be seen: (1) Section of one or both vagi may have no effect either on the hypertonic (spastic) pylorus or on the atonic pylorus. (2) Section of the vagi may be followed by prolonged relaxation of a hypertonic pylorus and by prolonged contraction of an atonic pylorus. (3) Tetanization of the peripheral end of the cut vagi always induces contraction of the atonic or moderately tonic pylorus, and may cause temporary or prolonged relaxation of the

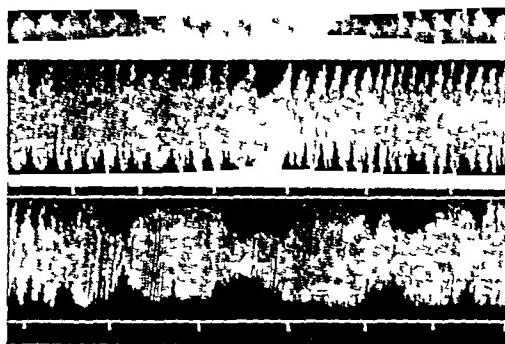


Fig. 2.—Water manometer tracings showing types of spontaneous rhythm of the pylorus in a dog under barbital anesthesia. Time in minutes.

hypertonic or spastic pylorus. Tracings illustrating some of these reactions are reproduced in Figure 3. At no time were the vagi nerves sectioned after prior section of the splanchnic nerves. These results seem to warrant the following interpretation or conclusion:

- (a) The vagus nerves send both motor and inhibitory efferents to the pylorus.
- (b) Protracted pylorospasm may in special cases be due to hyperactivity of the vagi motor system, since the spasm may decrease or disappear on section of the vagi.
- (c) Protracted atonicity may also be due to hyperactivity of the vagi inhibitory efferents, since section of the vagi may increase the tonus of an atonic pylorus.
- (d) The vagi inhibitory efferents are, at least in some cases, able to counteract a pylorospasm caused by other than vagi factors, since a spastic pylorus may be relaxed by tetanization of the peripheral end of the cut vagi.

We realize that these interpretations are not free from objections. Since the vagi efferents act also on the entire stomach, and possibly on the duodenal motor mechanisms, it is possible that some of the vagi effects on the pylorus outlined above in reality may be indirect effects from altered motor states of the stomach or duodenum. It is also possible that some of the immediate or temporary effects on the pylorus

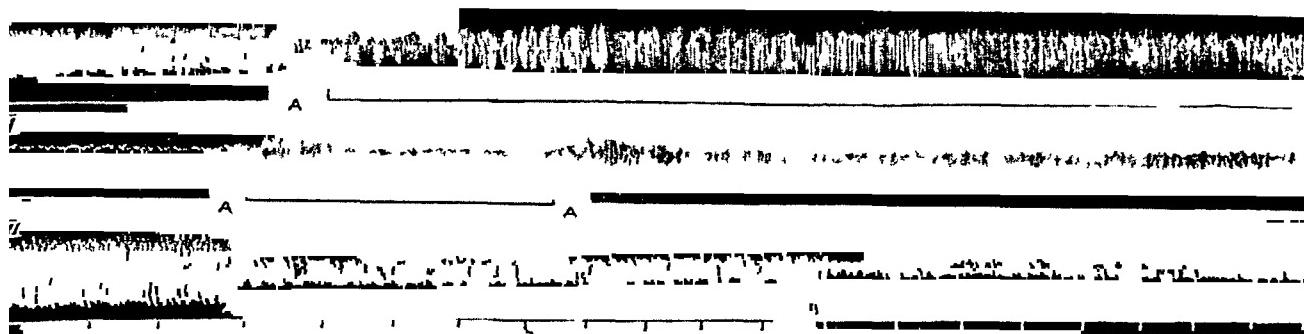


Fig 3.—Water manometer tracings of a dog under barbital anesthesia. Time in minutes. Ia, weak tetanization of peripheral end of the left vagus nerve in the neck, showing temporary tetanus of the pylorus followed by rhythmic contraction, IIa, pylorus in spasm, weak tetanization of the peripheral end of the vagus nerve in the neck, showing relaxation of the pylorus on vagus stimulation, III, atonic pylorus, a, section of the right vagus nerve, b, section of the left vagus nerve in the neck, showing increased tonus of the pylorus following section.

following section of the vagi in the neck are not due to section of motor and inhibitory efferents to the pylorus but to mechanical stimulation of vagi afferents and a reflex to the pylorus via the splanchnic efferents.

3. Influence of the Splanchnic Efferent Fibers on the Pylorus.—If the pylorus is atonic or in moderate tonus only, stimulation of the

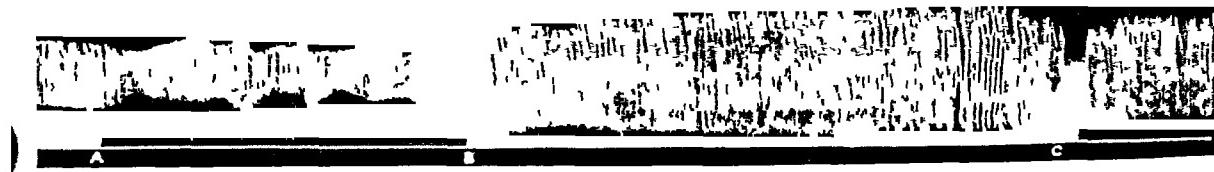


Fig 4.—Water manometer tracing of a dog under barbital anesthesia. a, beginning isolation of the left splanchnic nerves. b, section of the left splanchnic nerves. c, tetanization of the peripheral end of the left splanchnic nerves, showing tonic motor control of the splanchnic nerves on the pylorus.

peripheral end of the cut splanchnic nerves induces a marked contraction of the pylorus (Fig 4, c). It seems more difficult to secure clear inhibition of the pylorus or splanchnic stimulation, even when the pylorus at the time is hypertonic, but we have occasionally noted such inhibition. Our results are thus in complete agreement with those of

Thomas and Wheelon. The pylorus receives motor and inhibitory efferents both from the vagi and the splanchnics. The extrinsic efferent nerve supply to the pylorus and to the cardia is therefore identical both in character and source.¹

We have also occasionally noted marked relaxation of the hypertonic or moderately tonic pylorus following the section of one pair of splanchnic nerves (Fig. 4, b). This shows that in special cases hypertonus and spasm of the pylorus may be due to excess action of the splanchnic motor efferents.

4. Reflexes into the Pylorus from Stimulation of Visceral Sensory Nerves—(1) Mechanical or electrical stimulation of any visceral afferent nerve may induce a temporary spasm of the pylorus. We have thus obtained contractions of the pylorus by pressing on, sub-

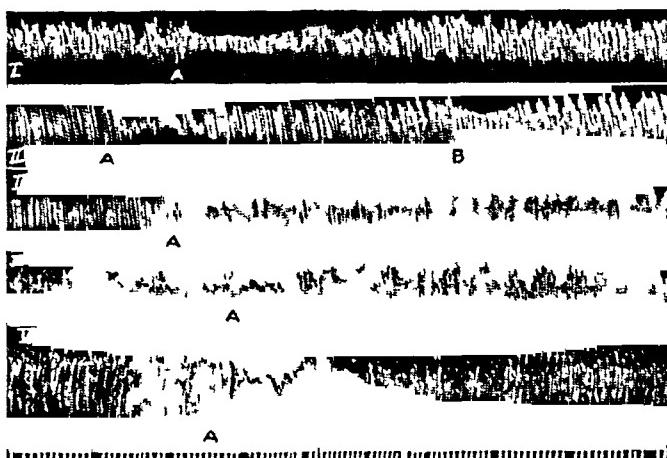


Fig. 5—Water manometer tracings of a dog under barbital anesthesia. Time in seconds. Ia, pressing on the wall of the urinary bladder, IIa, rubbing the parietal peritoneum, b, traction on the ureters, IIIa, pressing the large intestine between the fingers, IVa, pressing the left kidney between the fingers, Va, stretching the rectum by forceps through the anus. Showing reflex contraction of the pylorus by mechanical manipulation of the abdominal viscera.

bing, stretching or crushing the following organs: urinary bladder, ureters, kidneys, large and small intestines, mesenteric and parietal peritoneum. Since all of these reflexes into the pylorus persist after section of both vagi in the neck, it is evident that main efferent paths are in the splanchnic nerves. Stretching the anal sphincter or the rectum also causes a temporary pylorospasm (Fig. 5). So far we have not seen an inhibitory reflex into the pylorus from stimulation of visceral afferent nerves. The pylorospasms induced by these visceral irritations and traumas were always temporary, but they may outlast the stimulus by many minutes. We have not tried to elicit these pyloric reflexes after section of the splanchnic nerves or excision of the suprarenal gland to eliminate possible increased output of epinephrin as a

factor in the pylorospasm. It will be remembered that epinephrin induces contraction of the pylorus. This we confirmed on the dog.

It is thus clear that the pylorus and the cardia stand in the same reflex relation to the afferent nerves of the abdominal viscera.¹ The predominant reflexes from the viscera into these sphincters, under our experimental conditions, is motor, and if prolonged they become cardiospasms and pylorospasms.

5 Reflexes into the Pylorus from Stimulation of Spinal Sensory Nerves—Tetanization of the central end of the sciatic nerve produces a temporary spasm of the pylorus (Fig 6), even after section of both vagus nerves. In two experiments the sciatic stimulation induced relaxation of a spastic pylorus. Occasionally tetanization of the sciatic nerve induces a primary contraction of the pylorus followed by a marked but temporary depression of the tonus of the pylorus.

6 Reflexes into the Pylorus from the Gastric and the Duodenal Mucosa—In this phase of the work we were primarily interested in

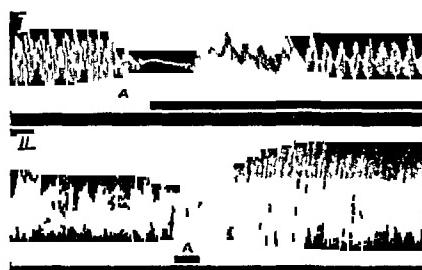


Fig 6.—Water manometer tracings of a dog under barbital anesthesia. Ia, strong tetanization of central end of sciatic nerve, showing tetanus of the pylorus followed by hypertonus, IIa, moderately strong tetanization of the central end of the sciatic nerve, showing increased tonus of the pylorus followed by relaxation.

determining to what extent the findings of previous investigators could be confirmed by these new experimental methods. Unless the pylorus is already in hypertonus or spasm, one never fails to secure contractions of the pylorus from anything and everything that stimulates the nerve endings in the duodenal mucosa. This pylorus reflex is induced by rubbing the duodenal mucosa with a probe, or a rubber tube, by slowly introducing from 5 to 10 cc of water, weak acids or weak alkalies (Fig 7). The pylorospasm induced by acid and alkalies in the duodenum is more marked than that induced by water in the duodenum. The stronger the acid or alkali, the stronger and the more prolonged is the pylorospasm.

These observations merely confirm those of previous investigators, beginning with Pavlov's pupil, Seidjukow. But we see no justification for calling this reaction an "acid reflex" specifically, since everything

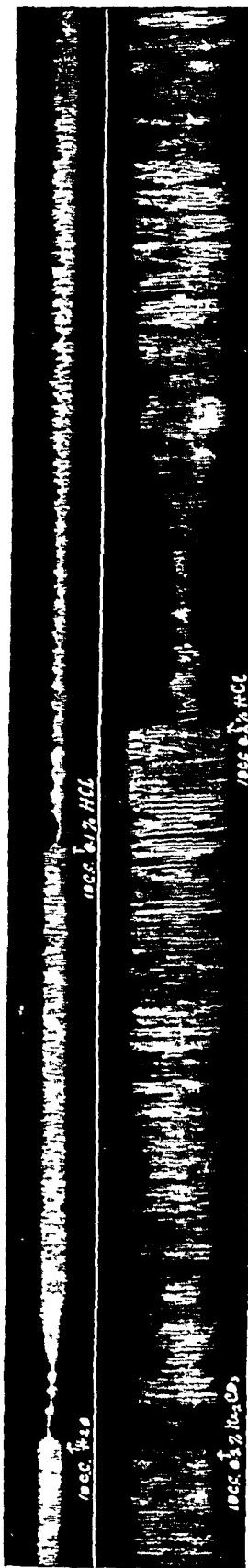


Fig. 7.—Water manometer tracings in a dog under barbital anesthesia. Ten cc. quantities of water, hydrochloric acid (0.1 per cent and 0.2 per cent), and sodium carbonate (0.2 per cent) into duodenum, showing reflex contraction of the pylorus from any fluid put into the duodenum

capable of stimulating the local nerve endings produces the reflex. We ordinarily do not call the retraction of the leg of the frog on irritating the skin of the toes with acids an "acid reflex."

If these duodenal nerve endings are hyperirritable, as in an ulcer region, they may be continuously stimulated not only by water and by acid or neutral gastric content, but also by the alkaline bile and pancreatic juice, and hence a more or less continuous pylorospasm may be induced.

It was shown by Brunemeier and Carlson⁹ (1915) that the stimuli in the duodenum that call forth contraction of the pylorus, induce at the same time (and by local reflex mechanisms) inhibition of the tonus and contractions of the empty stomach. Those who seek for teleologic relations may therefore call this a "protective reflex," the "gate" being shut and the driving power of the stomach reduced so that for a while at least no more irritating material enters the duodenum.

Under our experimental conditions water, acids (up to 0.2 per cent hydrochloric acid) or alkalis acting on the antrum mucosa had no effect on the tonus of the pylorus. This is true whether the pylorus was in hypertonus and spasm, in moderate tonus or atonic. These substances acting in the stomach caused neither relaxation nor contraction of the pylorus.

Our results, therefore, offer no support to the theory that acids acting on the antrum mucosa relaxes the pylorus. But negative results in animals under anesthesia do not necessarily refute positive findings by means of the roentgen-ray method on animals not under anesthesia. It seems, however, that our preparations should be no more abnormal than the excised and anemic stomach kept in oxygenated Ringer's solution, and Cannon has reported that acids on the stomach side open the pylorus in such preparations.

SUMMARY

A new method of accurate and continuous recording of the tonus and contractions of the pylorus is described, a method that seems to involve the minimum of local trauma consistent with accurate graphic recording. By this method on dogs under general anesthesia we find that

Motor and inhibitory nerve fibers enter the pylorus by way both of the vagi and of the splanchnic nerves (confirming previous observers).

There are types of pylorospasm that may be decreased or removed by (a) section of the vagus nerves, (b) by section of the splanchnic nerves, (c) by stimulation of the peripheral end of these nerves. There are states of atonicity of the pylorus that may be relieved by section

⁹ Brunemeier and Carlson Am Jour Physiol 36 191, 1915

of the vagus nerves. These facts indicate that states of spasm or atonicity of the pylorus may be caused by excess activity of either the vagus or the splanchnic efferents, motor and inhibitory.

Appropriate stimulation of all visceral sensory, and at least some spinal sensory (sciatic, sacral), nerves induces a temporary contraction or spasm of the pylorus. The vagus nerves are not necessary for this reflex.

Mechanical or chemical water, hydrochloric acid and sodium carbonate irritation of the duodenal mucosa causes contraction of the pylorus. It does not seem justified to designate this specifically as an "acid reflex." These stimuli, acting in the antrum under the same experimental conditions, do not influence the motor state of the pylorus.

Motor disturbances of the pylorus may thus be induced not only by local pathologic condition in the stomach and duodenum, or by abnormal states of the central nervous system, but also by excessive irritation of most, if not all, sensory nerves, particularly those of the abdominal viscera.

As a working hypothesis, the view is advanced that the action of visceral efferents (sympathetic and autonomic), at least on some of the motor mechanisms, are association or reflex responses and not simple peripheral responses like that of the skeletal muscles on stimulation of the pyramidal tract. That is, the visceral efferents are in reality afferents to local but diffuse reflex mechanism in the viscera. The prevailing view of simple antagonistic action of the vagus and the sympathetic systems is not tenable for the cardia, the stomach and the pylorus. Motor or inhibitory effects on these regions of the intestine are produced by both the vagi and the splanchnic systems, the character of the peripheral response depending on the initial physiologic state of the peripheral motor mechanism, analogous to the so-called "postural reflexes" of the spinal-skeletal system.

A COMPARISON OF NORMAL STANDARDS FOR THE VITAL CAPACITY OF THE LUNGS OF WOMEN*

RUTH E BOYNTON, MD

MINNEAPOLIS

Since the invention of the spirometer by John Hutchinson¹ in 1846, many valuable observations have been made by him and numerous other investigators on the vital capacity of the lungs in normal persons, as well as in those suffering from disease.

I shall not give a complete review of the literature on this subject, but references to certain important and closely related contributions will be given.

It is now an accepted fact that the vital capacity of a person is reduced in certain diseased conditions of the lungs, pleura and heart. The observations of Myers,² Garvin, Lundsgaard and Van Slyke,³ Ulrich and Nathanson,⁴ Wittich, Myers and Jennings,⁵ Peabody and Wentworth,⁶ Dreyer and Burrell⁷ and others have shown that there is a definite relation between the vital capacity of the lungs and the amount and type of the pathologic condition of the thoracic organs. Their studies also show that the vital capacity readings are an aid in rendering prognosis and in guiding a patient's activities.

This recognition of the value of vital capacity readings in clinical medicine has renewed the interest of investigators to determine satis-

* Read before the combined staffs of Lymanhurst School and Parkview Sanatorium, Minneapolis, June 26, 1923.

* From the Students' Health Service and the Department of Preventive Medicine and Public Health of the Medical School, University of Minnesota.

1 Hutchinson, John On the Capacity of the Lungs and on the Respiratory Functions with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, *Medico-Chir Trans* **29**, 1846.

2 Myers, J A Studies on the Respiratory Organs in Health and Disease IV A Comparison of Vital Capacity Readings and Roentgen-Ray Findings in Pulmonary Tuberculosis, *Tr National Tuberculosis Association*, New York, June, 1921, *Am Rev Tuberc* **5**, 1922 V A Comparison of Vital Capacity Readings and Physical Signs in Pulmonary Tuberculosis, *Minnesota Med* **5** 233 (April) 1922 VI The Significance of the Vital Capacity Test in Pulmonary Tuberculosis, Bronchial Asthma, Pneumonia and an Acute Infection Outside the Respiratory Tract, *Arch Int Med* **30** 648-667 (Nov) 1922

3 Garvin, A Lundsgaard, C, and Van Slyke, D Studies of Lung Volume II Tuberculous Men, *J Exper Med* **27** 87 (Jan) 1918 III Tuberculous Women, *J Exper Med* **27** 129 (Jan) 1918

4 Ulrich, H L, and Nathanson, M H The Vital Capacity of the Lungs in Cardiac Disease, *Minnesota Med* **4** 721 (Dec) 1921

5 Wittich, F W, Myers, J A, and Jennings, F L A Study of the Effect of Pulmonary Tuberculosis on Vital Capacity, *J A M A* **75** 1249 (Nov 6) 1920

6 Peabody, F W, and Wentworth, J A Clinical Studies of the Respiration IV The Vital Capacity of the Lungs and Its Relation to Dyspnea, *Arch Int Med* **20** 443 (Sept) 1917

7 Dreyer, G, and Burrell, L S T Vital Capacity Constants Applied to Pulmonary Tuberculosis, *Lancet* **2** 374 (Aug) 1922

factory standards for normal persons, for without these, obviously, variations from the normal cannot be accurately determined.

That the vital capacity varies according to the age, sex, height, weight, circumference of the chest, sitting height and habits of life of the normal person has been well established. Normal standards, based on a comparison of the vital capacity with these several factors, have been produced.

Hutchinson¹ concluded that the most reliable standard for estimating the vital capacity was the standing height. For every inch in increase of height between 5 and 6 feet, he estimated an increase in the vital capacity of 8 cubic inches of air. Hutchinson also noted the relation of the vital capacity to the body weight, but concluded that the variations in a normal standard were greater in comparing it to the weight than to the standing height.

Peabody and Wentworth⁶ also used the height of the person for their comparisons. They placed their normal persons in three groups, and the average vital capacity for each group was calculated.

A year later (1917) Lundsgaard and Van Slyke⁸ concluded that there was a more constant relationship between the vital capacity and the chest volume, calculated by measurements of the height, depth and breadth of the chest, than with any of the other standards which had previously been used.

Dreyer,⁹ in 1919, compared the vital capacity with the body weight, surface area, the stem height and the chest circumference.

The data presented in this paper were calculated from tables prepared by Myers¹⁰ from the mathematical formulas of Dreyer,⁹ the graphic chart of Du Bois and Du Bois,¹¹ and the observations of West¹² and Myers¹³.

⁸ Lundsgaard, C., and Van Slyke, D. D. Studies of Lung Volume I Relation Between Thorax Size and Lung Volume in Normal Adults, *Jour Exper Med* **27** 65 (Jan.) 1918.

⁹ Dreyer, G. *The Assessment of Physical Fitness*, New York, Paul B Hoeber, 1921.

¹⁰ Myers, J. A. Studies on the Respiratory Organs in Health and Disease VIII A Method for Quickly Obtaining the Percentage of an Individual's Theoretical Normal Vital Capacity of the Lungs, *Am Rev Tuberc* **7**, No 3 (May) 1923.

¹¹ Du Bois, D., and Du Bois, E. F. Clinical Calorimetry Tenth Paper A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known, *Arch Int Med* **17** 863 (June) 1916.

¹² West, H. F. Clinical Studies on Respiration VI A Comparison of the Various Studies for the Normal Capacity of the Lungs, *Arch Int Med* **25** 306 (March) 1920.

¹³ Myers, J. A. Studies on Respiratory Organs in Health and Disease II A Study of the Vital Capacity and Physical Fitness of Nurses with Tables Showing Calculated Vital Capacities for Normal Men and Women and a Method for Quickly Obtaining an Expression of an Individual's Physical Fitness *Journal-Lancet* **41** 252 (May) 1921.

The observations reported in this paper were made on a group of 738 college women at the University of Minnesota varying in age from 16 to 44 years. The measurements, with the exception of the vital capacity determinations which were made at the Students' Health Service, were taken at the Women's Gymnasium by the department of physical education at the time of a routine physical examination.

The standing height without shoes was recorded in inches, the weight without clothes in pounds and the stem height in inches.

The vital capacity in cubic centimeters was determined by means of a Sanborn water spirometer made according to the specifications of Peabody and Wentworth. A minimum of three trials was allowed and the highest reading recorded.

As the normal standards for women are based on observations on a comparatively small number of women, I felt that a comparison of a larger group of apparently normal women with the standards now accepted would be of value.

TABLE 1.—Percentage of Vital Capacity Calculated from Body Weight

Percentage of Vital Capacity	Number of Cases	Percentage of Cases
100 and over	283	48.84
90 to 99	215	29.11
80 to 89	142	19.24
70 to 79	84	11.38
60 to 59	9	1.21
50 to 59	5	0.67
Total	738	99.95

The percentage of vital capacity calculated from the body weight formula of Dreyer, the standing height, the surface area and the stem height was recorded for each woman. A total of 738 women were studied, although not all of the measurements were recorded on each of them.

In Table 1, the percentage of vital capacity calculated from the body weight by Dreyer's⁹ formula $\frac{W^{0.72}}{V^C} = K$ is recorded. The cases are grouped so as to compare the number and percentage of cases with the calculated vital capacity. Of a total of 738 cases, 498, or 77.45 per cent, were 90 per cent or more of the normal standard, and 240, or 22.55 per cent, were less than 90 per cent of the normal standard.

Data are presented in Table 2 showing the percentage of normal vital capacity calculated from the surface area. The surface area was calculated from the height and weight according to the method of Du Bois and Du Bois¹⁰ by means of tables prepared by Myers¹⁰.

Of a total of 480 cases, 311, or 64.4 per cent, were above 90 per cent of the normal standard, and 169 or 35.2 per cent, were less than 90 per cent of the normal.

West's¹² observations on eighty-five men and forty-four women, calculating the percentage of vital capacity from the surface area, showed only 55 per cent of the group less than 90 per cent of the normal. West's group contained both men and women, and there were a comparatively large number of men with athletic training, so that a comparison of the percentage of cases less than 90 per cent cannot be accurately made.

Table 3 shows a group of 593 cases with the vital capacity calculated according to the standing height by means of a table prepared by

TABLE 2—Percentage of Vital Capacity Calculated from Surface Area

Percentage of Vital Capacity	Number of Cases	Percentage of Cases
100 and over	155	32.2+
90 to 99	156	32.2+
80 to 89	109	22.7+
70 to 79	47	9.7+
60 to 69	11	2.2+
50 to 59	2	0.4+
Total	593	99.4+

TABLE 3—Percentage of Vital Capacity Calculated from Standing Height

Percentage of Vital Capacity	Number of Cases	Percentage of Cases
100 and over	114	19.2+
90 to 99	130	21.9+
80 to 89	175	29.5+
70 to 79	127	21.4+
60 to 69	41	6.9+
50 to 59	6	1.0+
Total	593	99.9+

TABLE 4—Percentage of Vital Capacity Calculated from Stem Height

Percentage of Vital Capacity	Number of Cases	Percentage of Cases
100 and over	59	11.9+
90 to 99	108	21.8+
80 to 89	141	28.6+
70 to 79	129	26.1+
60 to 69	45	9.1+
50 to 59	11	2.2+
Total	493	99.7+

Myers¹⁰ on the basis of the accepted standing height formulas. By this method, we find only 234 cases, or 41.1 per cent, that are 90 per cent or more of the normal standard and 349 cases, or 59.8 per cent, less than 90 per cent of the normal.

Peabody and Wentworth,⁶ in their studies of forty-four normal women, comparing the vital capacity with the standing height, found five cases, or 11.3 per cent, who were less than 90 per cent of the normal.

In Table 4, 493 cases from the same group of college women are classified according to their normal vital capacity calculated from stem

height measurements. The stem height was supposedly measured according to the method described by Dreyer. As I shall mention later in the paper, the possibilities of error in taking stem height measurements are great.

In the 493 cases in this group, 167, or 33.7 per cent, were 90 per cent or more than the normal standard, and 326, or 66.3 per cent, were less than 90 per cent of the normal standard.

The two outstanding things shown in this comparison are first the close relation between the percentage of vital capacity calculated from the body weight formula of Dreyer and from the surface area and the fact that with both methods over 65 per cent of the cases are more than 90 per cent of the normal standards, second, that, confirming the

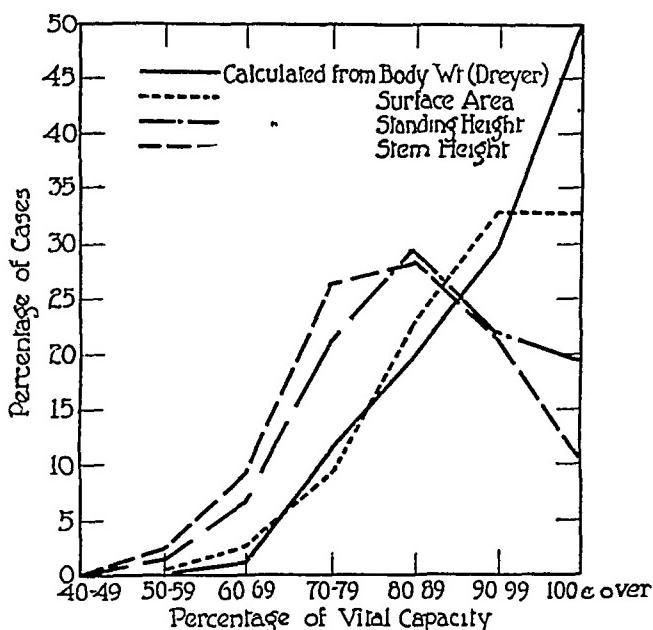


Chart 1.—The relation between the various methods of computing the normal vital capacity

observations of Rogers¹⁴ on a group of college men, the correlation between the stem height and vital capacity is no better than between the standing height and vital capacity. Also that apparently the normal standards for women for these two methods of computing the percentage of vital capacity are too high, since in both methods not more than 41 per cent of the cases are above 90 per cent of the normal.

Tables 5, 6, 7 and 8 group the persons examined according to age giving the number of cases in each age group and the average percentage of vital capacity in each age group, the vital capacity being calculated from the body weight formula of Dreyer, surface area, standing height and stem height.

14 Rogers, W. L. The Correlation of Vital Capacity with Stem Height, Arch Int Med 31: 342 (March) 1923.

TABLE 5.—Average Percentage of Vital Capacity Calculated from Body Weight Grouped According to Age in Years

Age	Number of Cases	Average Percentage Weight
16	33	91
17	136	97.41
18	198	95.17
19	119	95.38
20	63	98.12
21	30	97.33
22	24	93.16
23	14	95.92
24	8	102.87
25	4	116
26	7	92.71
27	4	95
28	3	89.66
29	3	94.66
30 and over	12	94.49
Total	658	

TABLE 6.—Average Percentage of Vital Capacity Calculated from Surface Area, Grouped According to Age in Years

Age	Number of Cases	Average Percentage Surface Area
16	23	85.5
17	130	94.3
18	158	93.6
19	117	92.7
20	60	93.4
21	27	93.1
22	17	89.8
23	11	90.7
24	10	92
25	3	95
26	7	84
27	3	86
28	3	86.3
29	3	89
30 and over	12	87
Total	584	

TABLE 7.—Average Percentage of Vital Capacity Calculated from Standing Height, Grouped According to Age in Years

Age	Number of Cases	Average Percentage Standing Height
16	25	81
17	127	89.7
18	164	88.3
19	117	87.05
20	61	87.86
21	27	86.07
22	17	85.35
23	12	90.42
24	9	90.66
25	3	88.33
26	7	77.14
27	4	84.75
28	3	78
29	3	82.66
30 and over	12	84.25
Total	591	

As we should expect with a group of persons at these ages, the curve of vital capacity percentages varies little between 16 and 30 years. The apparent decrease after 24 years of age is undoubtedly due to the small number of cases in those groups.

Chart 2 shows again the close relationship between the vital capacity calculated from the body weight formula of Dreyer and the surface

TABLE 8.—*Average Percentage of Vital Capacity Calculated from Stem Height, Grouped According to Age in Years*

Age	Number of Cases	Average Percentage Stem Height
16	25	75.2
17	139	85.4
18	177	82.5
19	123	82.1
20	65	82.6
21	29	81.8
22	20	78.4
23	13	90.5
24	11	77.5
25	4	77.2
26	8	70.3
27	6	83.3
28	3	73.3
29	4	78
30 and over	15	77.1
Total	642	

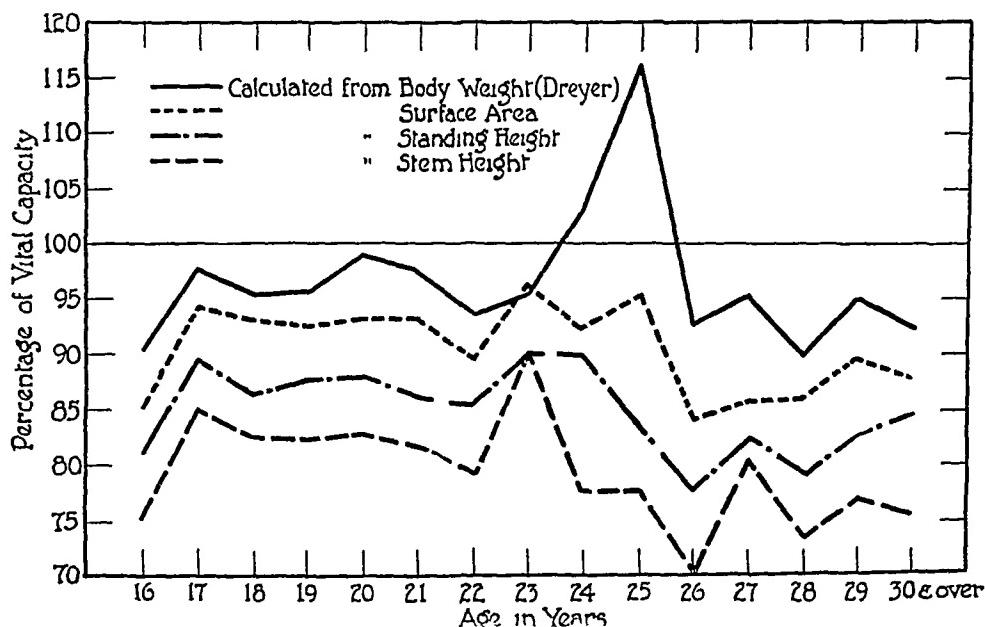


Chart 2.—Percentage of vital capacity according to age. Graphic representation of data contained in Tables 5, 6, 7 and 8.

area. With the exception of the sudden rise at age of 25 in the percentage by body weight, at no point do they differ by more than 7 per cent, the average variation being about 3 per cent. West¹² records a variation of 2 per cent in his cases.

We again see the standing height and stem height determinations running practically parallel but at a lower level than the other two. At the age of 23 years, the average vital capacity is 90 per cent, which is the highest recorded when computed from these measurements.

In assuming that the normal standard should be 100 per cent and a variation of 10 per cent on either side is to be considered within the limits of normal, from observations in this group of apparently normal persons, the present standards for women would seem to be too high, especially those for calculations from the standing height and stem height. It would seem desirable that a careful study and preparation of new normal standards be made after taking measurements on a larger group of women.

That the possibility of error in taking measurements of the stem height is greater than in the others recorded is obvious. As has been

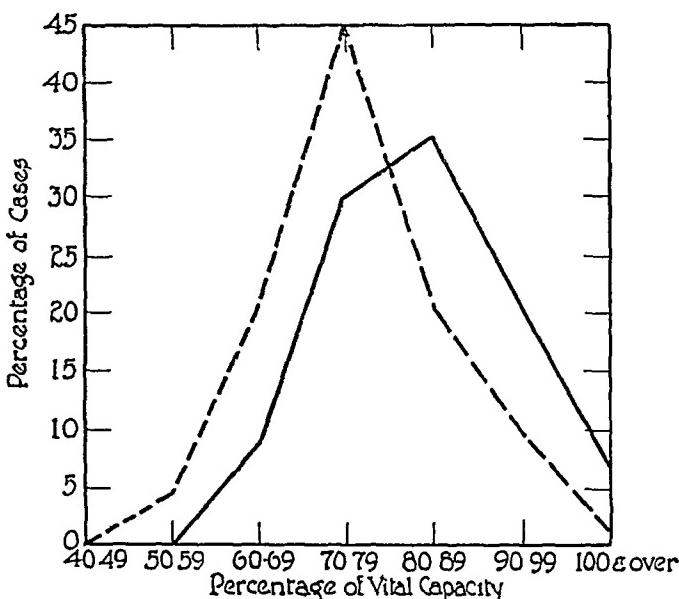


Chart 3.—This shows the great variation in the percentage of vital capacity calculated from two records of stem height on the same persons. The broken line indicates the curve calculated from measurements taken at the time of a routine physical examination, the continuous line is the curve calculated from measurements taken on the same persons at a special examination to recheck the vital capacity.

pointed out by others, the gluteal muscles may cause a variation of from 1 to 3 cm. We obtained data on a group of approximately 100 women, which illustrates clearly this possibility of error in recording the stem height. The stem height was measured at the time of a routine physical examination required for entrance to the University of Minnesota. The measurements were then taken by the department of physical education, supposedly according to the direction of Dreyer,⁹ but by persons not interested especially in the use of the measurements for calculating the percentage of vital capacity.

One hundred of these same women, a few weeks later, were examined at the Students' Health Service especially for a rechecking of the measurements and records for computing their vital capacity. The stem height measurements were taken by either a nurse or a physician who were vitally interested in procuring accurate data for statistical purposes.

Because of this possible source of error in taking the stem height and the comparative small source of error in recording the body weight and surface area, for practical clinical work in vital capacity determinations it would seem advisable to advocate simply the use of weight and body surface determinations to compute the percentage of normal of a person's vital capacity. For the scientist, the stem height measurements are of value and will, of course, continue to be used. In certain cases, especially when there is a disproportion between the standing height and length of the trunk, or in obese persons, the stem height measurements give a more accurate percentage of the person's normal vital capacity.

SUMMARY

1 From observations on a group of 738 college women, varying in age from 16 to 44 years, the normal standards for the percentage of vital capacity calculated from the body weight formula of Dreyer, surface area, standing height and stem height are apparently too high, especially for the standing height and stem height.

2 The correlation of the vital capacity with the body weight as calculated by Dreyer and with the surface area are approximately equal and the most reliable for ordinary use.

3 The correlation of the vital capacity with the stem height is no better than with the standing height among college women.

4 The possibility of error in measuring stem height is so great and in measuring body weight and height so small that for practical purposes the stem height measurements may be eliminated.

THE OCCURRENCE AND SIGNIFICANCE OF THE "MYELOBLAST" UNDER NORMAL AND PATHOLOGIC CONDITIONS

PRELIMINARY ACCOUNT

HAL DOWNEY, PH.D.

MINNEAPOLIS

The following paper is a brief account of the results of several years of investigation of the subject indicated in the title. The complete paper with detailed discussion of the literature will be published in some European journal, because the numerous colored plates will have to be lithographed.

Naegeli¹ (1900) was the first one to express the view that the non-granular cells of the marrow are specific parenchymatous cells of this tissue which serve as the parent cells for the granular leukocytes. Naegeli stated emphatically that although they possessed some lymphoid characters, they differed from true lymphocytes in their morphologic and biologic characters, and that their origin was entirely separate from that of the lymphocytes.

But Naegeli was not the first one to express the theory of a polyphyletic origin of the blood cells, and he was not the first one to describe lymphoid cells in the marrow. Ehrlich² had previously asserted that each type of blood cells had its own specific parent cell, and that these were not related, except through the embryonic mesenchyme.

The occurrence of lymphoid cells in the marrow was known to many authors previous to the announcement of Naegeli's myeloblast theory. Freiberg³ (1892) described lymphoid cells in the marrow of dogs. Arnold⁴ (1895) called attention to the fact that lymphoid cells occur in the marrow of frog and man, and Hirschfeld,⁵ in 1898, was the first

* Presidential address delivered before the Minnesota Pathological Society, May, 1923. From the Hematological Laboratory, Department of Animal Biology, University of Minnesota. Aided by a grant from the Research Funds of the Graduate School.

1 Naegeli, O. Ueber rotes Knochenmark und Myeloblasten, Deutsch med Wchnschr **26** 287, 1900. Blutkrankheiten und Blutdiagnostik, Berlin u Leipzig, Vereinigungswiss Verleger, 1919.

2 Ehrlich, P., and Lazarus, A. Die Anämie, Pt 1, Normale und pathologische Histologie des Blutes, 1898.

3 Freiberg, H. Experimentelle Untersuchungen über die Regeneration der Blutkörperchen im Knochenmark, Thesis, Dorpat, 1892 (Cited from Weidenreich.)

4 Arnold, J. Zur Morphologie und Biologie der Zellen des Knochenmarks, Virchows Arch f path Anat **140** 411, 1895.

5 Hirschfeld, H. Zur Kenntnis der Histogenese der granulierten Knochenmarkszellen, Virchows Arch f path Anat **153** 335, 1898. Ueber akute Leukämie, Folia Haematol **4** 202, 1907. Die unitarische und dualistische Auffassung über die Histopathologie der Leukämien, Folia Haematol **6** 382, 1908.

to claim that they differentiated into granular leukocytes He stated that these cells were not necessarily lymphocytes, although he could see no morphologic difference between them and true lymphocytes of the lymphatic tissues and blood Engel,⁶ Jolly,⁷ and Pappenheim⁸ also described lymphoid cells in the marrow previous to the birth of Naegeli's myeloblast Pappenheim, in 1899, stated that these lymphoid cells are identical with Troje's⁹ marrow cells and also with the lymphocytes of the blood and lymphatic tissues

Naegeli's view of the specific nature of the myeloblast was soon accepted by many, notably Schridde,¹⁰ but not all of those who accepted the dualistic view were willing to grant the existence of specific morphologic characters for the myeloblast which would always distinguish it from the lymphocyte or lymphoblast Michaelis and Wolff¹¹ (1901) describe "indifferent lymphoid cells" in the marrow which change to granular leukocytes They believe that lymphocytes, on the other hand, are differentiated lymphoid cells without the capacity for granular differentiation However, they could see no morphologic difference between lymphocytes and the indifferent lymphoid cells of the marrow Turk¹² (1904) designated the undifferentiated marrow cells as "lymphoid marrow cells" The only distinction between them and lymphocytes is the fact that the marrow cells differentiate while the lymphocytes do not There are no morphologic distinctions but they should be kept separate nevertheless Butterfield, Heineke and Meyer¹³ although

6 Engel, C S Weitere Beitrage zur Entwicklung der Blutkorperchen beim menschlichen Embryo, Arch f mikr Anat **53** 322, 1898

7 Jolly, J Recherches sur la division indirecte des cellules lymphatiques granuleuses de la moelle des os, Arch d'Anat Microscop **3** 168, 1899-1900

8 Pappenheim, A Vergleichende Untersuchungen über die elementare Zusammensetzung des roten Knochenmarks einiger Säugetiere, Virchows Arch f path Anat **157** 19, 1899 Atlas der menschlichen Blutzellen, Jena, G Fischer 1905-1912 Ueber die Deutung und Bedeutung einkerniger Leukocytenformen in entzündlichen Zellanhäufungen mit besonderer Rücksicht auf die lokale Eosinophilie, Folia Haematol **8** 1, 1909 Zur vorstehenden Mitteilung Dominici's, Folia Haematol **8** 107, 1909 Ueber die Wandlung des Lymphoidozytenbegriffs und der Blutstammzellen, Folia Haematol, Arch **21** 207, 1917 Morphologische Hamatologie, Leipzig, W Klinkhardt, 1919 Pappenheim, A, and Hirschfeld, H Ueber akute myeloide und lymphadenoide makrolymphozytäre Leukämie an der Hand von zwei verschiedenen Fällen, Folia Haematol **5** 347, 1908

9 Troje Cited from Pappenheim

10 Schridde, H Myeloblasten, Lymphoblasten und lymphoblastische Plasmazellen, Ziegler's Beitr z path Anat u z allgem Path **41** 223, 1907

11 Michaelis, L, and Wolff, A Die Lymphocyten, Deutsch med Wchnschr **27** 651, 1901

12 Turk, W Berichte aus den wissenschaftlichen Vereinen, Wiener med Wchnschr **54** 1430, 1904 Vorlesungen über klinische Hamatologie, Pt 1, Wien, 1904 Ueber die Beziehungen zwischen myeloidem und lymphatischem Gewebe im Verlaufe von Leukämien, Verh d Kongr f innere Med **23** 585, 1906

13 Butterfield, E E, Heineke, A, and Meyer, E Ueber das Vorkommen der Altmannschen Granulationen in den weissen Blutzellen, Folia Haematol **8** 325, 1909

accepting the dualistic view, state that all of the morphologic characters claimed for the lymphoblast by Naegeli and Schmidde are also to be found in the myeloblast, including the Altmann-Schmidde granules.

Helly¹⁴ (1910) follows the old Ehrlich view and believes that the myelocyte is the most primitive type of granular cell in the marrow. He states that granular leukocytes are derived from nongranular cells normally only in the embryo. In pathologic human and experimental mammalian marrow he finds them only in cases showing signs of anemic degeneration, and he, therefore sees in them signs of an exhausted process of blood formation. Most of them are dedifferentiated erythroblasts, but some are dedifferentiated neutrophil myelocytes and some are ordinary lymphocytes.

Opposed to the dualistic and polyphyletic views is the unitarian or monophyletic theory of the origin of blood cells. According to this view, all of the blood cells are related and they are all descended from one type of parent cell. The extreme unitarian view as represented by Maximow,¹⁵ Weidenreich,¹⁶ Danchakoff¹⁷ and their followers, accepts the lymphocyte as this parent cell, but according to Pappenheim,⁵ Ferrata¹⁸ and their school, the parent cell is the myeloblast of Naegeli which in the normal adult is to be found in the bone marrow only. The lymphocyte is descended from this "lymphoidocyte," as Pappenheim calls it, in the embryo, while the lymphocytes of the adult are maintained by partially differentiated lymphoblasts of the lymphatic tissue and organs. Pappenheim recognizes the possibility of relations between granular leukocytes and lymphocytes by way of the dedifferentiated lymphocyte which has reverted to the lymphoidocyte stage and is then capable of differentiating into a granular leukocyte. For the normal adult Pappenheim is willing to admit that the cell which Naegeli described as a myeloblast is to be found only in the marrow, but, nevertheless, it may show relationships with the lymphocytes, for it may occur in the acute lymphatic leukemias, and lymphocytes are derived from it in the embryo.

14 Helly, K. Kritik der sogenannten Myeloblasten, Verhandl d. deutsch. path. Gesellsch. **14** 198, 1910. Aamische Degeneration und Erythrogramien, Ziegler's Beitr. z. path. Anat u. allgem. Path. **49** 15, 1910.

15 Maximow, A. Der Lymphozyt als gemeinsame Stammzelle der verschiedenen Blutelemente in der embryonalen Entwicklung und im postfetalen Leben der Säugetiere, Folia Haematol. **8** 125, 1909. Experimentelle Untersuchungen zur postfetalen Histogenese des myeloïden Gewebes, Ziegler's Beitr. z. path. Anat u. Allgem. Path. **41** 122, 1907.

16 Weidenreich, F. Die Leukocyten und verwandte Zellformen, Wiesbaden, J. F. Bergman, 1911.

17 Danchakoff, V. Origin of the Blood Cells. Development of the Haematopoietic Organs and Regeneration of the Blood Cells from the Stand-point of the Monophyletic School, Anat Rec. **10** 397, 1916.

18 Ferrata, A. Le emopatie, Milano, Società Editrice Libraria **1**, 1918.

Maximow¹⁵ and Weidenreich¹⁶ do not agree with this view, they deny the existence of the myeloblast and lymphoidocyte and claim that there is abundant evidence for the differentiation of granular leukocytes and erythrocytes from the true lymphocyte. The so-called myeloblast is merely a temporary variation form of the lymphocyte, which is of no significance, or the structure which has been described for it is the result of the dry smear method on which most of the descriptions of this cell are based. With the section method they can see no difference between lymphocytes and the nongranular cells of the marrow.

Maximow admits that in newly born animals there are certain differences between myeloblasts and lymphoblasts, but these differences are slight, and the differences between the myeloblasts are often greater than those between myeloblasts and lymphoblasts, and they are not sufficient to justify sharp division between the two. They may be accounted for by the different mediums in which the cells are located.

No one who has worked with the blood from a case of myelogenous leukemia will agree with Maximow's and Weidenreich's denial of the existence of the cell described by Naegeli as the "myeloblast." On the other hand, there has accumulated a large body of evidence in favor of their view of the possible derivation of granular leukocytes from true lymphocytes. The following may be cited as examples of this type of evidence.

Delamare¹⁹ (1901) found eosinophil myelocytes in the follicles of normal lymph nodes of rabbits and pigs. The nuclei of these myelocytes resembled those of lymphocytes both in size and distribution of chromatin. All intermediate stages between lymphocytes and polymorphonuclear eosinophils were found, and some of the cells contained only a few granules. He also found nucleated reds within the follicles of a mesenteric lymph node of a gray rat.

Stschastny²⁰ (1905) obtained general and local eosinophilia by injections of foreign erythrocytes and hemolytic serums. Mononuclear eosinophils were found in the peritoneal exudate, in the lungs, lymph nodes and spleen. Their nuclei resembled those of large mononuclears and lymphocytes. Typical myelocytes were not found.

Dominici²¹ obtained the differentiation of myelocytes within the follicles and germ centers of lymph nodes and spleen of rabbits with

19 Delamare, G. Note sur les cellules eosinophiles et les hématoïdes nucléés du ganglion lymphatique normal, C R de la Soc de Biologie **53** 849, 1901.

20 Stschastny, S. M. Ueber die Histogenese der eosinophilen Granulationen im Zusammenhang mit der Hamolyse, Ziegler's Beitr z path Anat u z allgem Path **38** 456, 1905.

21 Dominici, H. De l'origine lymphatique ou amyeloïde des polynucléaires ou leucocytes granuleux à noyau polymorphe, Folia Haematol **8** 97, 1909. Etudes sur le tissu conjonctif et les organes hematopoïétiques des mammifères Arch d'Anat Microscop **17** 1, 1921.

experimental infections and repeated bleedings. He also noted myeloid metaplasia of the lymphocytes of the taches laiteuses of the omentum of rabbits infected with taeniae, and this observation was confirmed by Pappenheim.

Maximow¹⁵ ligated the vessels of the kidney, an operation which resulted in the production of bone and bone marrow within the kidney. The myeloid cells of the marrow could be traced to the lymphocytes which migrated from the vessels. Some of these lymphocytes began their differentiation to granular leukocytes while they were still in the vessels. Recently Maximow has obtained the differentiation of lymphocytes from cultures of lymph nodes grown with cell-free bone marrow extract.

Weidenreich and I²² described and figured the differentiation of small and medium sized lymphocytes to granular leukocytes in the lymph nodes of the weasel. The small myelocytes were of special significance, for they were of the size of small lymphocytes, and their nuclei had exactly the same structure and the same amount of chromatin as the nuclei of the surrounding small lymphocytes. Typical myelocytes with pale nuclei were also noted in the same preparation. This checks with Dominici's observation that lymphocytes can differentiate into granulocytes without change in their inner nuclear characters or the nuclei may change to the myelocyte type, giving two types of mononuclear granulocytes. The myelocytic type is the common one for the marrow, while the lymphocytic type is more frequent in the tissues.

According to Weidenreich and Weill²³ myelocytes are common in the hemolymph nodes of sheep and other animals and in the normal mucosa of the digestive tract and in the thymus of adult man. They derive these cells from lymphocytes.

I have obtained myeloid metaplasia of lymphocytes of all types in the omentum of rabbit surrounding a graft of foreign tissue, and I have also confirmed Dominici's observation of the occurrence of myelocytes within the follicles of lymph nodes of rabbits which have been bled repeatedly.

Recently one of my students, Dr Logefield, observed extremely small myelocytes, no larger than a small lymphocyte, with small dark

22 Downey, H., and Weidenreich, F. Ueber die Bildung der Lymphozyten in Lymphdrusen und Milz, Arch f mikr Anat **80** 306, 1912.

23 Weill, P. Ueber die Bildung von Leukozyten in der menschlichen und tierischen Thymus des erwachsenen Organismus, Arch f mikr Anat **83** 305, 1913. Ueber die Bildung von granulierten Leukozyten im Karzinomgewebe, Virchows Arch f path Anat **226**, No 2, 1919. Ueber die leucocytaren Elemente der Darmschleimhaut der Säugetiere, Arch f mikr Anat **93** 1 1919. Ueber das regelmässige Vorkommen von Myelocyten in der Milz des erwachsenen Menschen, Arch f mikr Anat **93** 82, 1919.

nuclei absolutely identical with those of the surrounding small lymphocytes in a case of mixed leukemia

These facts, and many more which might be cited, prove beyond question that lymphocytes may under certain conditions differentiate into myeloid cells, that is, granular leukocytes and red cells. Normally, this may occur to a limited extent in the thymus and intestine, but not in lymph nodes or human spleen.

However, these facts do not dispose of the myeloblast as readily as many of those who hold the unitarian view seem to think, for, as every pathologist knows, a cell of that structure does exist, at least in the leukemic blood. But it does not necessarily follow that the cell is a myeloblast in Naegeli's sense, that is, it does not have to be a cell which occurs in the normal marrow and only in the marrow. It may be an atypical pathologic cell type which does not occur in the normal person, or it may be a dedifferentiated myelocyte or erythrocyte, as claimed by Helly. Naegeli believes that the cell is specific for the marrow and that it is in no way related to the lymphocyte. I shall discuss his statements one at a time.

NAEGELI'S THEORIES

Morphologic—Naegeli's morphologic criteria for distinguishing the myeloblast have undergone considerable change since 1900, the distribution of the nuclear chromatin in the form of a delicate network being the only one of the original Naegeli characters to stand the test of time. Absence of nucleoli in the myeloblast was at first one of its distinguishing features, but now Naegeli claims that the myeloblast has from two to four nucleoli and the lymphoblast one to two. Butterfield,²⁴ Schridde¹⁰ and others have shown that the number of nucleoli is inconstant for the individual cells of the two types. It still remains a fact, however, that on the average the myeloblasts have smaller, more rounded and more numerous nucleoli, while the nucleoli of lymphocytes are usually not so numerous, are larger and more irregular in outline and more deeply stained.

Naegeli states that the granules which may occur in myeloblasts are unripe neutrophil granules and not azure granules, as is claimed by other workers. Few agree with Naegeli on this, but many recognize a special type of myeloid azure granulation which may occur in myeloblasts and leukoblasts, but not in lymphocytes.

Naegeli made much of the Schridde fuchsinophil granules which were supposed to be specific for lymphoblasts until Butterfield, Meyer

²⁴ Butterfield, L. E. Ueber die ungranulierten Vorstufen der Myelocyten und ihre Bildung in Milz-, Leber- und Lymphdrusen, Deutsch Arch f klin Med 92: 336, 1908.

and Hemeke¹³ and Wallgren²⁵ showed that they can occur in myeloblasts also. They have been shown to be mitochondria which may occur in all blood and tissue cells and are, therefore, not specific for any one type of cell. According to Naegeli's latest view, these granules occur in lymphoblasts and myeloblasts of smears, but not in the myeloblasts of sections. Those in the myeloblasts are in the form of short threads or commas, while those of the lymphoblasts are short rods located in the perinuclear area.

Biologic Differences—Proteolytic and oxydase ferments occur in myeloblasts but not in lymphoblasts. Sometimes the oxydase is absent from myeloblasts, but this is due to injury of the cell.

I have not investigated the oxydase reaction, but a few statements from the literature are of interest.

M. L. Menten²⁶ concludes that the reaction is an adsorption phenomenon dependent on properties of intracellular surfaces. It is not specific for myeloid cells, for lymphocytes give a well marked reaction, although the reaction is stronger in eosinophil and neutrophil leukocytes. Many tissues give the reaction, so it is by no means specific for blood cells.

Hynek²⁷ refers to a case of myelogenous myeloblastic leukemia in which the myeloblasts did not give the reaction, and he also refers to a case of Decastello in which the reaction was negative.

Klein²⁸ showed that lymphocytes also give the reaction, and W. Schulze²⁹ found that the myeloblasts of the normal marrow usually do not give the reaction, while the pathologic myeloblasts in blood and organs in myeloblastic leukemia are usually positive.

Citron³⁰ states that negative oxydase reaction is frequently found in undoubted myeloid-leukemic changes, and so it does not determine the myeloid or lymphatic nature of the condition. Positive reaction proves myeloid cell nature existing at the time, but does not tell us anything of the genesis of these myeloid cells, as from previously negatively reacting lymphocytes.

Histologic Differences—Myeloblasts are found normally only in the marrow, never in lymphatic organs, especially not in follicles or germ

25 Wallgren, A. Zur Kenntnis der lymphoiden Zellen des Kaninchenblutes, *Folia Haematol* **8** 307, 1909.

26 Menten, M. L. A Study of the Oxydase Reaction with Alpha-Naphthol and Para-Phenylenediamine, *J. M. Res.* **40** 433, 1919.

27 Hynek, K. Zur Monozytenfrage, *Folia Haematol*, *Arch* **13** 345, 1912.

28 Klein, S., cited from E. Neumann *Virchows Arch f path Anat* **207** 379, 1912.

29 Schulze, W. Zur Differentialdiagnose der Leukämien, *Munchen med Wochenschr* **56** 167, 1909.

30 Citron, J. Ueber zwei bemerkenswerte Fälle von (akuter) Leukämie, *Folia Haematol*, *Arch* **20** 1, 1915.

centers Under no circumstances are myelocytes ever developed in the follicles and germ centers of lymph nodes and spleen When myeloid metaplasia occurs it is always in the pulp or interfollicular and medullary tissue of lymph nodes The myeloid and lymphatic tissues are antagonistic to one another, if one hypertrophies, the other is suppressed or crowded out In myelogenous leukemia the follicles are reduced or entirely suppressed, while in lymphatic leukemia there is a great overgrowth of follicles at the expense of the pulp and medullary tissue

These are complex questions, and their complete discussion would require many pages However, a few statements from the literature with some observations of my own and of my students will prove that there is something to be said on the other side of these questions

First, in regard to the statement that myeloblasts and myelocytes can never occur in the follicles Dr H Z Giffin³¹ has reported a case of persistent eosinophilia in which I have found eosinophil myelocytes in the germ centers of the follicles of the spleen, and myelocytes were observed by Dominici and myself in the follicles of lymph nodes of rabbits which had been bled repeatedly Roman³² observed myelocytes in the germ centers of tonsillar follicles and also in the germ centers of the follicles of a cervical lymph node in a case of myelogenous chloroleukemia This is not interpreted as an invasion of the germ centers from the outside, because there were few myelocytes in the immediate vicinity of the follicles In spite of the fact that the author is a dualist, he interprets his findings as indicating true myeloid metaplasia of the germ centers

That myeloblasts may also occur in the follicles was shown by Citron³⁰ and by one of my students, Dr Fineman³³ Both of these cases were cases of lymphatic leukemia in which most of the lymphoid cells of the blood were of the myeloblastic type In Citron's case the marrow was normal and the myeloblasts were seen to be coming from the follicles and germ centers as well as from other parts of the nodes Fineman was unable to get marrow from his case, because necropsy was not permitted, but a lymph node removed at biopsy during the height of the proliferative activity showed the myeloblastic type of cell all through the node Clinical observation of the case permits the assumption that all of the cells of myeloblastic type which were noted in the blood were coming from the lymph nodes rather than from the marrow, for there was no evidence of increased marrow activity

³¹ Giffin, H Z Persistent Eosinophilia with Hyperleucocytosis and Splenomegaly, Am J M Sc **158** 618, 1919

³² Roman, B Zur Kenntnis der myeloischen Chloroleukämie, Ziegler's Beitr. z path Anat u z allgem Path **55** 61, 1913

³³ Fineman, S A Study of Microlymphocytic Leukemia, Arch Int Med **29** 168 (Feb) 1922

The supposed antagonism between the lymphatic and myeloid tissues is the strongest point urged by the dualists in favor of their view of the specific myeloid nature of the myeloblast. At first thought this argument seems difficult to meet, but this is true only when one fails to consider all of the known facts in the case. The literature contains many observations against this view, and I and my students can add more.

Werzberg³⁴ and Hertz,³⁵ studying experimental myeloid metaplasia, showed that myeloid metaplasia may occur at a time when there is hypertrophy of the follicles. Sternberg³⁶ states that in myelogenous leukemia the relative abundance of pulp and follicles of the spleen is extremely variable. In some cases both pulp and follicles are equally enlarged, and in others the hypertrophy involves either the follicles or the pulp. The pulp may be greatly increased and the follicles only slightly so, or the follicles may be completely suppressed. Myelocytes may occur in the follicles. Follicles of lymph nodes may also contain myelocytes, especially in their peripheral parts.

Isaac and Cobliner³⁷ report two cases in which the blood was that of chronic lymphatic leukemia, while the histologic changes of the organs were those commonly found in myelogenous leukemia. Pappenheim states that myelogenous leukemia may occur with a normal marrow, and lymphatic leukemia may be centered in the marrow leaving the lymph nodes normal.

Hirschfeld⁵ cites a number of cases of acute leukemia which show all of the intermediate stages between acute lymphatic and acute myelogenous leukemia. He concludes that this is proof for the correctness of the unitarian view, and that this view gives the only explanation for these variations in the character of the cases cited.

Cases of so-called mixed leukemia, that is, cases in which the lymphatic and myeloid tissues show equal activity, are of special importance in deciding this question. Such cases have been reported by Decastello,³⁸ Turk,¹² Hirschfeld,⁵ Herxheimer³⁹ and A. Herz.⁴⁰ In

34 Werzberg, A. Neue experimentelle Beiträge zur Frage der myeloïden Metaplasie, *Virchows Arch f path Anat* **204** 272, 1911.

35 Hertz, R. Zur Frage der experimentellen myeloischen Milz-Metaplasie, *Zeitschr f Klin Med* **71** 435, 1910.

36 Sternberg, C. Primärerkrankungen des lymphatischen und hamatopoietischen Apparates, normale und pathologische Morphologie des Blutes, *Ergeb d allgem Path u path Anat (Lubarsch-Ostertag)* **9** 360, 1905.

37 Isaac, S., and Cobliner, S. Ueber mikrolymphozytare Typen akuter myeloischer Leukämien, *Folia Haematol*, *Arch* **10** 459, 1910.

38 Von Decastello, A. Ueber Leukopenie und kleinalymphozytare Umwandlung des Knochenmarkes bei chronischer myeloischer Leukämie und bei Sepsis, *Folia Haematol*, *Arch* **13** 471, 1912.

39 Herxheimer, G. Ueber einen kombinierten Fall von lymphatischer und Myeloblastenleukämie, *Zentralbl f allgem Path* **24** 897, 1913.

40 Herz, A. Zur Frage der gemischten Leukämie, *Wiener klin Wochenschr* **22** 1030, 1909. Die akute Leukämie, Leipzig, F. Deuticke, 1911.

spite of the pronounced activity of both systems, these authors, except Hirschfeld, thought that the two remained distinct and separate. One of our own cases, however, which has just been worked over by Dr. Logefeld, shows free mixing of the cells of the two systems. The liver shows the changes characteristic of lymphatic leukemia. Portions of the spleen show extensive myeloid metaplasia, but in other parts there is a decided overgrowth of lymphatic tissue. In the lymph nodes there is diffuse lymphatic increase accompanied by myeloid metaplasia. The leukemic infiltration of the lungs, kidneys and pancreas consists of lymphocytes and myelocytes freely mixed. The blood of this case is also mixed, and it is evident that both myelocytes and lymphocytes are derived from the myeloblast. The diagnosis of mixed leukemia was first made from the blood and the organ changes were found to be just as anticipated from the blood findings.

These reports from the literature and our own findings are surely not in line with the usual dualistic conception of the antagonism of the one tissue for the other. One of the strongest arguments of the dualists, therefore, falls to pieces.

RESULTS OF AUTHOR'S RESEARCHES

But the myeloblast of Naegeli as a cell type still remains. I have already presented some evidence to indicate that this cell is not a specific bone marrow cell. My personal investigation of this question extending over several years has uncovered more facts in favor of this view. It is this work which I now wish to consider briefly.

The question is too complex to be solved by the use of any one method or of any one type of material. The conflicting views on this subject are undoubtedly due largely to the fact that past work has been too one-sided. The anatomists have relied on the section method and have failed to study the pathologic material. Pathologists and clinicians on the other hand, have pinned their faith to the pathologic material, largely human, and seem to have forgotten that normal tissues and organs are still to be had. Some are also unaware of the fact that anatomists and histologists have worked on blood and have even written about it.

In my own work I have tried to avoid the foregoing objections by utilizing a great variety of normal, pathologic and experimental material and by considering all of the available literature.

It seems almost axiomatic that in a problem of this kind one should turn first to the normal tissues, but curiously this side of the problem is the one which has received the least attention in the past.

In the course of the work it soon became evident that the section method is the least reliable. By this method the finer nuclear structures which we are accustomed to see in the blood smears disappear, and it

is indeed difficult if not impossible to distinguish between the lymphocytes of lymph nodes and the lymphoid cells of the marrow. Fine smears of marrow and lymph nodes can be obtained if they are fixed in Helly's fluid while they are still moist and then treated as though they were sections. But even with this method it is impossible to distinguish the finer details, and therefore impossible in many cases to compare tissue cells with cells of the blood smears as usually prepared. After much work with this method it was finally abandoned in favor of the dry smear method as practiced for blood smears with Wright's stain. It was impossible to overcome the difficulty of making satisfactory dry smears of marrow and lymph nodes, but by making them in large numbers and selecting only the best slides abundant good material was obtained.

The results of the work on normal human and mammalian organs can be summarized briefly:

(1) Myeloblasts exist in the normal marrow of human and mammalian adults. They occur in small numbers, because blood regeneration is largely homoplastic. They are far more numerous in the young and new-born in whom heteroplastic regeneration is more pronounced. They do not occur in lymph nodes and spleen nor in the normal blood. The peculiar myeloid type of azure granulation described by Pappenheim and others and frequently noted in the myeloblasts of the leukemic blood was found in the myeloblasts of human marrow, but not in those of rabbits.

(2) Myeloblasts occur in the blood and lymph nodes in small numbers in newly born rabbits. The human new-born has not yet been investigated with reference to this particular question.

(3) We have several cases of acute lymphatic leukemia with myeloblasts in the blood and tissues. In these cases all intermediate stages lead from the myeloblast to fully matured lymphocytes, so there can be no doubt that there are relations between them.

(4) We also have two cases of mixed leukemia in which both lymphocytes and myeloid cells are derived from the myeloblasts of the blood. Organ changes which have already been described correspond to the blood findings.

CONCLUSIONS

These observations justify the following conclusions:

(1) Incomplete morphologic dualism exists in the normal mammalian and human adult. The myeloblast is a real stem cell of the myeloid cells of the marrow. Lymphocytes of lymph nodes and spleen are regenerated by mitosis of their own kind and by derivation from the reticulum without the intervention of the myeloblast. The lymphocyte has not lost its capacity for further differentiation, as is evidenced

by the fact that normally some of those located in the intestinal mucosa, thymus and hemolymph nodes may differentiate into granular leukocytes. The differentiation of tissue mast cells and plasma cells from lymphocytes is also a well-known process.

(2) Under pathologic and experimental conditions which cause myeloid metaplasia the derivation of myeloid cells from lymphocytes without the intervention of the myeloblast may be an extensive process.

(3) In the myelogenous and acute lymphatic leukemias the myeloblast may serve as the stem cell of both lymphocytes and myeloid cells, and this may take place in the same person in cases of mixed leukemia. For the myeloid series this can be accounted for by the differentiation of cell types which normally exist in the marrow, but for the lymphocytes the relation with the myeloblast must be explained by factors which do not exist in the normal person. Dedifferentiation of the lymphocytes to the myeloblast, which is the equivalent of the primitive blood cell of the embryo, at least so far as one can judge from sections, may be one factor. Excessive liberation of free cells from the reticulum with retardation or complete failure of differentiation may be another factor. Evidence for this was obtained from Dr Fineman's³³ case of lymphatic leukemia, in which many of the myeloblasts of the node could be traced to the fixed tissue. Under normal conditions the nuclei of such cells change rapidly, even before the cells have become free, but in this case they remained practically identical with those of the fixed cells of the reticulum. Such nuclei are of the myeloblastic type. These myeloblasts show all transitions to lymphocytes, as was proved by Fineman,³³ and true lymphocytes undoubtedly result from their differentiation. This may also be true of the few lymphocytes which occur normally in the bone marrow, although no one has succeeded in working this out for the normal marrow.

The position of the myeloblast may now be defined with some accuracy. It probably corresponds to the primitive blood cell of the embryo and is retained in the normal adult only in the marrow, where it is primarily related to the cells of the myeloid series. In newly born rabbits it also occurs in limited numbers in the blood and lymphatic tissues. In the leukemias it may revert to its primitive relations with the fixed tissue on the one hand and the lymphocytes and myeloid cells on the other.

The lymphocyte is to be regarded as a specialized or partly differentiated cell endowed with myeloid potentialities which usually do not develop, but which may do so when the proper stimulus is applied, in other words, their function and structure is not a fixed entity as is the case with the mature myeloid cells.

It is interesting to note that Naegeli,¹ who is the chief defender of the dualistic view, is at heart a unitarian. The following statement

occurs in the third edition of his handbook "When myeloid cells occur in lymphatic tissue they are always of perivascular origin from indifferent mesenchyme cells. The same is true of lymphocytes when they occur in myeloid tissue. The blood vessels are surrounded by indifferent mesenchyme cells which in the adult may differentiate in either direction."

THE VALUE OF CAFFEIN AS AN ANTIDOTE FOR MORPHIN^{*}

CHARLES C HASKELL, MD, J E RUCKER, BS
AND

W S SNYDER, JR, BA
RICHMOND, VA

A study of the combined action of two drugs is of both theoretical and practical interest. From the practical standpoint, the result of such a study may shed light on the value of either drug in the abnormal states encountered in disease, with more certainty, it may give information regarding the efficacy of one drug as a physiologic antidote for the other. The comparative frequency of morphin poisoning, the frequent subcutaneous administration of the poison and the fact that considerable time may elapse before the patient comes under treatment, all combine to render it desirable that we possess a satisfactory physiologic antidote against morphin. For this purpose, several drugs have been proposed, of these, caffein alone seems to have met with almost universal approbation. The present investigation was undertaken to ascertain whether this favorable view could be supported by experimental evidence.

EXPERIMENTS WITH MORPHIN AND CAFFEIN PERFORMED ON CATS

The first experiments were carried out on cats. Using a method essentially the same as that described by Hatcher and Brody¹ for the assay of digitalis, the attempt was made to ascertain the fatal dose of morphin sulphate for these animals by slow intravenous injection. The cats were lightly etherized for operation, and a cannula, connected with a buret containing a solution of morphin sulphate, 1 per cent in physiologic sodium chlorid solution, was inserted into the femoral vein. The morphin sulphate solution was injected at the rate of 1 c c per kilogram of body weight every two minutes until the death of the cat appeared imminent, when the rate of injection was materially reduced. Somewhat to our surprise, it was found, by the use of nine cats, that the lethal dose of morphin administered in this way did not vary widely, the average being 390 mg of morphin sulphate per kilogram of body weight, the extremes, 310 and 440 mg per kilogram.

Salant and Rieger² state that the average minimum lethal dose of caffein administered orally to cats is 150 mg per kilogram of body

* From the Laboratory of Pharmacology, Medical College of Virginia

1 Hatcher, R A, and Brody, J G The Biological Standardization of Drugs, Am J Pharmacy 82 360 (Aug) 1910

2 Salant, W, and Rieger, J B The Toxicity of Caffein, Bull 148, Bureau of Chemistry, U S Dept of Agriculture

weight Pilcher³ has observed death to follow a dose of 60 mg per kilogram, but evidently he regards this as exceptional, placing the average minimum lethal dose at about 120 mg per kilogram. Although it is possible that season or locality may influence the resistance of cats to caffein intoxication, the assumption that 80 mg of caffein per kilogram, administered orally in the form of a 1 per cent solution of the base, would prove fatal only in exceptional cases seemed justifiable. Consequently, this dose was given to each of a series of six cats, and in from fifteen to thirty minutes, the animals were etherized and given the morphin injections as in the preceding series in which morphin alone was used. The average amount of morphin sulphate required to cause the death of these "caffeinized" cats was less than that necessary for the untreated animals, being 303 for the former and, as previously stated,

TABLE 1.—*Lethal Dose of Morphin Alone or with Caffein Given Cats by Intravenous Injection*

Weight of Cat in Kg	Dose of Caffein in Mg per Kg	Dose of Morphin in Mg per Kg	Average
2.0	0	310	
2.9	0	310	
2.8	0	390	
3.4	0	390	
2.3	0	410	
2.3	0	410	
3.4	0	420	
2.1	0	430	
2.5	0	440	
3.5	80	230	
2.9	80	290	
2.5	80	310	
3.8	80	310	
3.1	80	320	
2.4	80	360	
			303

390 mg per kilogram for the latter. So far as one may draw conclusions from so limited a number of experiments, a large, but not necessarily fatal, dose of caffein lowers the resistance of cats to the toxic action of morphin. The condensed protocols of these experiments are given in Table 1.

An effort was made to determine the average minimum lethal dose of morphin sulphate injected subcutaneously into cats. Sollmann, quoting Mueller,⁴ states that the fatal dose of morphin for cats varies from 40 to 80 mg per kilogram. In our experiments, four of the seven cats that received 20 mg of morphin sulphate per kilogram alone succumbed, while the animals that were given doses of 25, 30, 35, and 40 mg per kilogram survived.

³ Pilcher, J. D. Alcohol and Caffein. A Study of Antagonism and Synergism, *J. Pharmacol. & Exper. Therap.* 3: 267 (Jan.) 1911-1912.

⁴ Sollmann, T. A Laboratory Guide in Pharmacology, Philadelphia, W. B. Saunders Company, 1917.

On the other hand, of the nine cats that were given 20 mg of morphin and from 15 to 20 mg of caffein, seven died, and two cats died that received 30 and 35 mg per kilogram of morphin sulphate, respectively, in conjunction with 20 mg of caffein per kilogram. The results are summarized in Table 2.

Table 2 shows that the mortality following a dose of 20 mg of morphin sulphate per kilogram alone is a little more than 57 per cent, but when the animal receives 15 or 20 mg of caffein per kilogram, the mortality is increased to a little more than 77 per cent. Moreover, the cats that were given 25, 30, 35 and 40 mg of morphin alone survived, while doses of 30 and 35 mg of morphin per kilogram proved fatal when combined with a dose of 20 mg of caffein per kilogram.

TABLE 2.—*Lethal Dose of Morphin Alone or with Caffein Given by Subcutaneous Injection into Cats*

Weight of Cat in Kg	Caffein in Mg per Kg	Morphin in Mg per Kg	Result
1.72	0	20	Survived
2.10	0	20	Survived
2.07	0	20	Survived
2.21	0	20	Died
1.70	0	20	Died
2.04	0	20	Died
2.33	0	20	Died
1.81	0	25	Survived
1.51	0	30	Survived
1.96	0	35	Survived
2.04	0	40	Survived
2.41	20	20	Survived
2.33	15	20	Survived
1.59	20	20	Died
1.70	20	20	Died
1.81	20	20	Died
2.07	20	20	Died
2.90	15	20	Died
1.99	15	20	Died
2.47	15	20	Died
2.27	20	30	Died
2.50	20	35	Died

EXPERIMENTS WITH MORPHIN AND CAFFEIN PERFORMED ON GUINEA-PIGS

It is a well-known fact that morphin causes excitement in the cat and that death often occurs during convulsions. Caffein also has this effect on cats, so that it would seem quite possible that caffein might act deleteriously in morphin poisoning in cats, and, on the other hand, exert a favorable influence where this apparent synergism is absent. For this reason, guinea-pigs were selected for the next experiments.

Sollmann⁴ states that the average lethal dose of morphin sulphate for guinea-pigs is about 700 mg per kilogram when the drug is injected subcutaneously. According to our experience, however, the dose is appreciably less than this during the winter and early spring, the time when our experiments were carried out. Injected in the form of a 1 per cent solution in saline, the minimum fatal dose at this time was

found to be about 500 mg per kilogram. Two pigs succumbed after a dose of 400 mg per kilogram, but this appears to be exceptional.

Salant and Rieger² found that the average minimum lethal dose of caffeine by subcutaneous injection into guinea-pigs was from 200 to 240 mg per kilogram of body weight, while doses of 100 to 120 mg per kilogram caused "no manifestation of nervous or muscular disturbance nor any departure from the normal in respiratory activity." To eliminate the possibility of a variation according to season or diet (our experiments were carried out in November), a few guinea-pigs were given

TABLE 3.—*Lethal Dose of Morphin and of Caffein Alone and in Combination Given in Subcutaneous Injection into Guinea-Pigs*

Weight of Pig in Kg	Morphin in Mg per Kg	Caffein in Mg per Kg	Result
0 455	350	0	Survived
0 210	400	0	Survived
0 320	400	0	Died
0 390	400	0	Died
0 415	400	0	Survived
0 570	400	0	Survived
0 465	400	0	Survived
0 545	400	0	Survived
0 460	450	0	Survived
0 770	450	0	Survived
0 595	450	0	Survived
0 400	450	0	Survived
0 665	450	0	Survived
0 600	500	0	Survived
0 610	500	0	Died
0 235	500	0	Died
0 340	500	0	Died
0 555	500	0	Died
0 555	500	0	Died
0 405	550	0	Died
0 360	550	0	Died
0 420	0	100	Survived
0 360	0	100	Survived
0 500	0	270	Survived
0 475	0	300	Survived
0 435	0	330	Died
0 265	500	100	Died
0 500	500	100	Died
0 475	400	100	Died
0 250	400	100	Died
0 500	330	100	Died
0 520	330	100	Died
0 451	250	100	Survived

caffeine subcutaneously in the form of a 1 per cent solution in saline. In agreement with the observations of Salant and Rieger, it was found that a dose of 100 mg per kilogram produced no detectable change in the pigs, and it was necessary to administer more than 300 mg per kilogram before death of the animal ensued. It seems fair to assume, therefore, that 100 mg of caffeine per kilogram injected subcutaneously into guinea-pigs is by itself nontoxic. In a third series of pigs, however, it was found that the injection of this amount of caffeine appreciably lowered the resistance of the animals to morphin intoxication, the average lethal dose of morphin sulphate for the pigs receiving 100 mg of caffeine per kilogram being reduced from 500 to 330 mg or less per kilogram. These results are given in Table 3.

EXPERIMENTS WITH MORPHIN AND CAFFEIN PERFORMED ON
WHITE MICE

In the next experiments, white mice were utilized. According to Hunt⁵ the average minimum fatal dose of morphin sulphate for white mice is 600 mg per kilogram, but the resistance of the animals is influenced much by adventitious factors. During November, we found

TABLE 4.—*Lethal Dose of Morphin and of Caffein Alone and in Combination Given in Intraperitoneal Injection into White Mice*

Weight of Mouse in Kg	Morphin in Mg per Kg	Caffein in Mg per Kg	Result
17.3	300	0	Survived
15.5	300	0	Survived
24.0	300	0	Died
20.0	350	0	Survived
16.5	350	0	Survived
19.0	350	0	Died
17.0	350	0	Died
20.0	350	0	Died
17.5	400	0	Survived
20.0	400	0	Survived
18.0	400	0	Died
14.5	450	0	Died
19.5	450	0	Died
16.0	500	0	Died
25.0	500	0	Died
22.5	550	0	Died
24.0	550	0	Died
25.2	0	160	Survived
19.8	0	160	Survived
22.5	0	180	Survived
21.1	0	180	Survived
17.7	0	180	Survived
23.0	0	180	Survived
18.5	0	180	Survived
18.0	0	180	Died
25.4	0	200	Survived
23.0	0	200	Survived
12.5	0	200	Survived
30.3	0	200	Died
20.0	0	200	Died
16.5	0	200	Died
15.0	0	220	Died
16.5	0	220	Died
21.0	0	250	Died
16.5	0	250	Died
24.0	300	150	Survived
17.6	300	150	Survived
25.3	300	150	Died
22.0	330	120	Died
15.5	330	120	Died
23.0	330	120	Died
24.0	330	110	Died
18.0	330	110	Died

that the minimum lethal dose for the animals kept on an oat diet was in the neighborhood of 350 mg per kilogram, no mouse surviving a dose of 450 mg of morphin sulphate per kilogram. As in the experiments on guinea-pigs, a 1 per cent solution of morphin sulphate in saline was employed, but with the mice, the injections were made intraperitoneally.

5 Hunt, Reid. The Effects of a Restricted Diet and Various Diets Upon the Resistance of Animals to Certain Poisons, Bull. 69, Hyg. Lab., U. S. P. H. S.

Hale⁶ puts the minimum lethal dose of "caffein citrate" at 700 mg per kilogram in white mice, when the method of administration is subcutaneous. Using a 1 per cent solution of the free base in saline and making the injections intraperitoneally, we placed the minimum fatal dose at about 200 mg per kilogram. Hale's dose is equivalent to about 350 mg per kilogram, the difference between this amount and that found necessary by us is probably referable to the different method of administration.

When from 55 to 75 per cent of the estimated minimum lethal dose of caffein is injected into white mice, there appears to be a definite reduction in the resistance of these animals to morphin poisoning. As previously mentioned, the average minimum lethal dose of morphin sulphate alone for white mice when injected intraperitoneally is about 350 mg per kilogram, but when caffein is used in the amounts mentioned, the lethal dose of morphin seems to be between 300 and 330 mg per kilogram. When morphin alone was used, two of the three mice receiving doses of 400 mg of morphin sulphate per kilogram survived; in the caffein-morphin series, no mouse survived a dose of 330 mg. These results on mice are given in Table 4.

COMMENT

From these experiments, it appears that caffein, either in large amounts or in doses quite comparable to those sometimes employed clinically, instead of proving an effective antidote for morphin poisoning, actually exerts an unfavorable action. This is in harmony with the results of Hale⁶ and of Pilcher,³ the former finding that caffein appeared to enhance the toxicity of acetanilid, and the latter that caffein lessened the chances of recovery from severe ethyl alcohol poisoning. It was suggested in both these cases that the undesired synergism was exerted on the heart, in fact, Hale secured tracings which supported this view for caffein and acetanilid. A similar depressant action on the heart appears to be the explanation for the unfavorable results with caffein and morphin, the evidence in support of this will be presented elsewhere in a more technical discussion of the problem.

That a deleterious action would result from the use of caffein in a human being suffering from morphin poisoning cannot be stated positively. Quantitatively, there is a vast difference in the action of morphin on man and on any of the animals used in this investigation. It is possible that the respiratory center of man is peculiarly sensitive to the action of morphin, so that death in human beings would result from doses of morphin which affect the circulation little or not at all, while,

⁶ Hale, Worth. The Influence of Certain Drugs upon the Toxicity of Acetanilide and Antipyrine, Bull 53, Hyg Lab, U S P H S

on the other hand, in the lower animals, the larger doses necessary to cause death involve the heart muscle also. If this is the case, it is conceivable that caffeine, by combating the respiratory depression which is the chief or sole factor in clinical morphine poisoning, may be of value as a physiologic antidote. It is generally assumed that morphine is practically free from a depressant action on the circulation when used clinically, so far as we are aware, no observations have been reported concerning the condition of the heart in clinical morphine poisoning. It would be of great interest to ascertain whether large doses of morphine depress the heart in human beings, such knowledge would enable us to draw more satisfactory conclusions regarding the rôle of caffeine in the treatment of clinical poisoning by morphine sulphate.

CLINICAL OBSERVATIONS ON THE DYNAMICS OF VENTRICULAR SYSTOLE

II HYPERTENSION *

H S FEIL, MD, AND L N KATZ, MD

CLEVELAND

The phases of ventricular systole have been fully studied in the experimental animal under various dynamic conditions Wiggers,¹ in a recent critical report, not only analyzed the effect of general arterial constriction, but also studied the results of aortic compression at different points. The isometric period under increased arterial resistance was, in most cases, unaltered, although occasionally it was shortened, and when the aorta was compressed near the semilunar valves, the isometric period was lengthened. The ejection phase was shortened by increasing the arterial resistance except when it was associated with considerable systolic retention in the ventricle. Under the latter conditions, the ejection phase was lengthened. On this basis of experimental data we might anticipate certain clinical findings in hypertension. With an efficient heart, elevation of blood pressure should cause no change or slight lengthening of the isometric period and a shortening of the ejection phase. In a failing heart, with its attendant venous congestion, lengthening of both phases should follow. How closely anticipated effects follow dynamic changes in man may be judged from our observations.

Weitz² studied the duration of the cardiac phases in man under various pathologic conditions. He utilized the apex beat in measuring these periods—a method that is not free from error. In the few hypertension cases that he analyzed he noted an occasional lengthening of the isometric period, with the ejection phase shorter than the normal at corresponding rates. Meakins³ noted that left ventricular preponderance and high blood pressure were frequently associated with a prolonged S-T interval. Fenn,⁴ in a recent study found systole unchanged in many cases of hypertension, but noted a distinct lengthening in others. As he used only the Q-T interval, his results hold only for total systole or, more precisely, for electrical systole.

* From the Medical Clinic of Western Reserve University at City Hospital
1 Wiggers, C J Am J Physiol **56** 415, 1921

2 Weitz, W Deutsch Arch f klin Med **127** 325, 1918

3 Meakins, J C Prolonging of "S-T" Interval of Ventricular Complex as Shown by Electrocardiograph Arch Int Med **24** 489 (Nov) 1919

4 Fenn, G K Studies in Variation of Length of Q-R-S-T Interval, Arch Int Med **29** 441 (April) 1922

The method employed in our present observations was the same as that described in a previous paper⁵. Figure 1 is a typical example of the records from which the duration of systole and its component phases were obtained. The upper curve inscribes the heart sounds, the middle curve the subclavian arterial pulse, and the electrocardiogram (Lead II) is below. In all, twenty-four cases were studied. Clinical observations and blood pressure readings were made at the time of the graphic registration. These data are tabulated in Table 1, arranged according to heart rate (Column 3), which in this series ranged from 46 to 127 beats per minute with a corresponding cycle length (Column

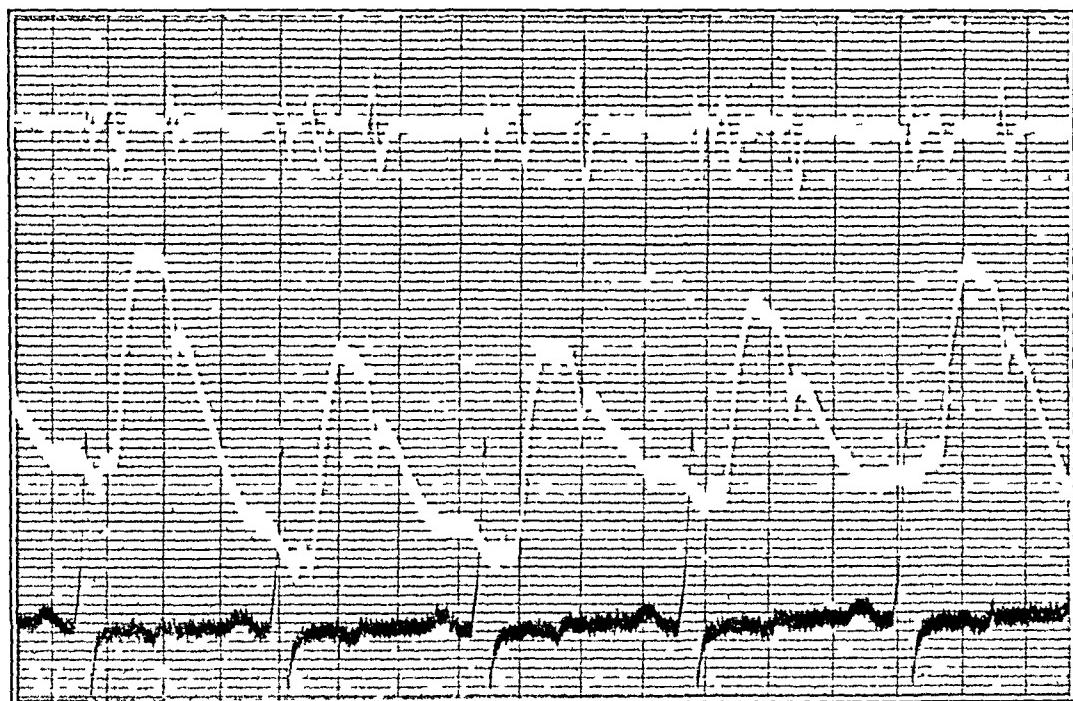


Fig. 1.—Simultaneous record of heart sounds (upper curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II (bottom curve), used in this series. The duration of the component phases of cardiac systole were determined by the method described in a previous paper. Time in fifths of a second.

4) varying from 0.392 of a second in Case 1 to 1.572 of a second in Case 24. In Columns 5, 6, 7 and 8 are given respectively the durations of diastole, total systole, isometric contraction and systolic ejection. The time relation of these phases to the heart rate are, with one or two exceptions, the same as in the normal series reported by us elsewhere⁵.

5 Katz, L. N., and Feil, H. S. Clinical Observations on the Dynamics of Ventricular Systole I. Auricular Fibrillation, Arch. Int. Med. 32: 672 (Nov.) 1923.

ISOMETRIC PERIOD

An analysis of Table 1 shows that the isometric period usually falls within the normal range, that is, from 0.03 to 0.07 of a second in many instances, namely, Cases 3, 4, 5, 6 (a), 6 (b), 6 (c), 6 (d), 8 (a), 9, 12, 14 (a), 14 (b), 16, 18 and 19, but in all these cases it is in the upper limits of normal. In other persons it is slightly longer (namely, Cases 1, 2, 7, 10, 11, 17 and 22), and in still others it is distinctly longer than normal (namely, Cases 13, 15, 20, 21, 23 and 24). An example of a record in which the isometric period varied from 0.07-0.09 of a second is shown in Figure 1.

In Table 1, we have indicated in Columns 10, 11, 12, 13 and 14 our clinical observations on the patient (age, systolic and diastolic blood pressure, etc.). A further study of this part of the table shows that this lengthening in hypertension bears no definite relation to the age, the height of either the systolic or diastolic blood pressure, the condition of the arteries, the degree of failure or the cause of the hypertension. Like the isometric phase in normal persons, it is independent of the heart rate and the duration of the other cardiac phases. The independence of the isometric period in regard to these factors confirms the opinion expressed before⁵ that its duration depends primarily on the physiologic condition of the myocardium and is therefore an index of the rate of contraction of the heart.

EJECTION PHASE

When the duration of ejection in Table 1 is compared with the theoretical value obtained as we explained in a previous paper (compare Columns 8 and 9) one notes that in most instances the ejection period is less than normal, that is, the difference between Column 8 and Column 9 is greater than 0.05 of a second (namely Cases 3, 4, 5, 6 (a), 6 (b), 6 (c), 6 (d), 7, 8 (b), 9 (b), 10, 14 (a), 14 (b), 17, 20, 21, 22 and 24). This abbreviation of ejection is illustrated in Figure 1, in which the difference between actual systole and the calculated systole is 0.09 of a second. In several this difference falls within the normal range (namely, Cases 1, 2, 11, 12, 13, 15, 16, 19 and 23), and in Case 18 it is distinctly longer than normal. When the relative shortening was analyzed from the point of view of the other variables (that is, height of systolic and diastolic blood pressure, condition of the palpable arteries, etiology of the hypertension and age of the patient) it was found to be unrelated to any of them, but it did bear a definite relation to the degree of cardiac failure, as shown in Table 2. For example, eight had a relatively reduced ejection. In fact, in Cases 9 and 14 (a) and (b) this occurred despite the lowering of the blood pressure to normal limits—the result of cardiac failure. In eleven patients without

TABLE I—Duration of Systole and Its Phases in Hypertension

Case	Number of Beats Measured	Heart Rate (60/C)	Aver age	Duration of Cycle	Devi ation from Average	Duration of Diastole	Devi ation from Average	Duration of Systole	Devi ation from Average	Duration of Isometric Contraction		Duration of Systolic Ejection		Grehl 'S', from Formulas $\leq V_0 31 C$	Sclerosis of Pal pable Arteries	Degree of Cardiac Failure	
										10	11	12	Blood Pressure	Man	Min imum Sys tolic		
1 R 1†	5	127	0 470	+0 075 -0 078	0 175	+0 067 -0 050	0 275	+0 029 -0 023	0 081	+0 014 -0 019	0 194	+0 021 -0 021	0 213	D H S	65	104	++
2 C S *	8	117	0 510	+0 014 -0 010	0 257	+0 007 -0 011	0 233	+0 011 -0 006	0 070	+0 007 -0 006	0 171	+0 011 -0 011	0 221	Neph	10	235	--
3 J M	19	115	0 522	+0 016 -0 011	0 316	+0 013 -0 010	0 206	+0 024 -0 016	0 017	+0 014 -0 014	0 159	+0 026 -0 022	0 224	Neph	22	158	-3
4 H 1†	7	114	0 525	+0 1 0 -0 1 0	0 302	+0 072 -0 119	0 223	+0 070 -0 028	0 002	+0 019 -0 011	0 161	+0 024 -0 014	0 25	D H S	72	210	++
5 M O'N	7	114	0 527	+0 010 -0 011	0 336	+0 007 -0 008	0 191	+0 015 -0 017	0 062	+0 011 -0 009	0 120	+0 004 -0 008	0 235	D H S	29	198	±
6(a) B B	9	113	0 531	+0 006 -0 005	0 337	+0 006 -0 007	0 194	+0 006 -0 010	0 064	+0 008 -0 009	0 130	+0 007 -0 010	0 226	D H S	43	190	+
6(b) B B	8	110	0 548	+0 006 -0 006	0 341	+0 006 -0 059	0 310	+0 010 -0 002	0 202	+0 006 -0 005	0 110	+0 002 -0 004	0 270	D H S	43	190	+
7 B S †	14	105	0 567	+0 063 -0 059	0 341	+0 066 -0 055	0 310	+0 010 -0 002	0 226	+0 011 -0 009	0 080	+0 009 -0 010	0 233	D H S	34	220	-
8(1) J W1	22	101	0 596	+0 025 -0 028	0 294	+0 022 -0 025	0 262	+0 014 -0 021	0 063	+0 021 -0 014	0 139	+0 026 -0 032	0 239	D H S	32	210	++
9 E S	12	101	0 597	+0 068 -0 058	0 371	+0 050 -0 052	0 226	+0 037 -0 029	0 058	+0 020 -0 017	0 168	+0 017 -0 017	0 239	D H S	46	112	86**
10 A Wo†	6	99	0 604	+0 004 -0 004	0 342	+0 008 -0 014	0 262	+0 016 -0 007	0 073	+0 006 -0 010	0 180	+0 010 -0 010	0 241	D H S	35	2 0	++
11 L O §	7	99	0 605	+0 005 -0 004	0 326	+0 007 -0 008	0 279	+0 005 -0 007	0 082	+0 012 -0 005	0 195	+0 016 -0 007	0 211	Neph	30	190	--
12 A W1¶	6	99	0 607	+0 019 -0 024	0 346	+0 019 -0 018	0 261	+0 011 -0 007	0 048	+0 005 -0 006	0 213	+0 006 -0 010	0 241	D H S	42	230	--
13 W K°	5	96	0 621	+0 011 -0 008	0 282	+0 007 -0 007	0 339	+0 009 -0 003	0 132	+0 007 -0 003	0 244	+0 003 -0 003	0 244	Neph	27	210	--

14(γ) J Wa	19	96	0 625	+0 026	0 424	+0 025	0 201	+0 026	0 070	+0 028	0 131	+0 013	0 245	D H S	55	130	95**	±	
8(b) J Wi	5	90	0 657	+0 004	0 377	+0 003	0 280	+0 006	0 093	+0 003	0 187	+0 004	0 251	D H S	52	200	140	++	
6(c) B B	6	89	0 670	+0 007	0 457	+0 008	0 213	+0 005	0 071	+0 008	0 142	+0 010	0 254	D H S	43	190	140	+	
6(d) B B	6	88	0 678	+0 022	0 425	+0 021	0 243	+0 020	0 055	+0 021	0 188	+0 006	0 256	D H S	43	160	120	+	
15 F B	6	87	0 687	+0 014	0 366	+0 014	0 321	+0 016	0 094	+0 006	0 227	+0 019	0 257	D H S	30	165	130	-	
16 A I	6	84	0 715	+0 004	0 16	+0 004	0 28	+0 012	0 066	+0 010	0 223	+0 011	0 262	Neph	37	210	140	±	
17 A S	5	82	0 729	+0 017	0 450	+0 038	0 279	+0 033	0 078	+0 022	0 201	+0 004	0 265	D H S	25	170	100	-	
18 N R	5	80	0 753	+0 011	0 405	+0 015	0 348	+0 009	0 054	+0 006	0 294	+0 003	0 269	D H S	56	190	110	+	
19 M W #	7	79	0 762	+0 038	0 465	+0 037	0 297	+0 015	0 061	+0 010	0 236	+0 012	0 271	D H S	16	165	120	-	
11(b) J Wa	6	78	0 773	+0 021	0 517	+0 015	0 226	+0 006	0 047	+0 012	0 179	+0 015	0 273	D H S	55	130	95**	±	
20 J D	c	76	0 791	+0 020	0 481	+0 013	0 313	+0 010	0 091	+0 003	0 222	+0 013	0 276	Neph	36	190	110	-	
21 W Mc	8	73	0 823	+0 062	0 508	+0 058	0 315	+0 014	0 100	+0 015	0 215	+0 008	0 281	D H S	56	185	122	++	
22 D H	13	69	0 861	+0 145	0 567	+0 123	0 294	+0 039	0 079	+0 051	0 215	+0 024	0 283	D H S	54	165	100	+	
23 Z Z ††	11	68	0 880	+0 024	0 506	+0 027	0 374	+0 018	0 129	+0 016	0 245	+0 017	0 291	Neph	39	220	120	+	
24 A Wi	6	46	1 295	+0 277	0 940	+0 272	0 355	+0 015	0 091	+0 012	0 261	+0 007	0 352	D H S	50	160	100	++	

In Columns 4, 5, 6, 7 and 8 the first figure is the average of the record measured the plus and minus figures are the variation above and below the average D H S indicates diffuse vascular sclerosis, Neph, chronic nephritis

* QRST interval -0 305 (+0 017, -0 005)

† QRST interval -0 274 (+0 011, -0 008)

‡ QRST interval -0 279 (+0 017, -0 039)

§ QRST interval -0 378 (+0 017, -0 033)

|| QRST interval -0 325 (+0 028, -0 019)

○ QRST interval -0 339 (+0 012, -0 011)

■ QRST interval -0 365 (+0 035, -0 014)

▲ QRST interval -0 374 (+0 026, -0 021)

◆ QRST interval -0 460 (+0 003, -0 013)

†† Blood pressure at other times much higher

failure the duration of ejection was normal in seven instances, reduced in three and increased in one. In four cases with slight failure, ejection was reduced in three and normal in one instance.

TOTAL SYSTOLE

Like the ejection phase, total systole is abbreviated in cardiac failure. This effect is anticipated when one considers that the duration of total systole is largely determined by the length of ejection. The relation of total systole to heart rate is shown in Figure 2, which is made up of

TABLE 2.—*The Relation of the Duration of Total Systole to the Degree of Cardiac Failure*

1 Case Number	2 Heart Rate	3 Blood Pressure	4 Degree of Cardiac Failure	5 Duration of Total Systole†	6 Duration of Systolic Ejection‡
1	127	162/104	None	+	N
2	117	235/175	None	N	N
7	105	220/136	None	N	-
11	99	190/120	None	N	-
12	99	230/120	None	N	N
13	96	210/140	None	+	N
15	87	165/130	None	+	N
17	82	170/100	None	N	-
18	80	190/110	None	+	N
19	79	165/120	None	+	+
20	76	190/110	None	N	-
3	115	158/128	Slight	-	-
21	73	185/122	Slight	N	-
22	69	165/100	Slight	N	-
23	68	220/120	Slight	+	N
4	114	210/120	Considerable	N	-
5	114	198/160	Moderate	-	-
6 (a)	113	190/140	Considerable	-	-
6 (b)	110	190/140	Considerable	-	-
6 (c)	89	190/140	Considerable	-	-
6 (d)	88	160/120	Considerable	-	-
8 (a)	101	240/140	Considerable	-	-
8 (b)	90	200/140	Considerable	N	-
9	101	112/86*	Considerable	-	-
10	99	250/165	Considerable	N	-
14 (a)	96	130/95*	Moderate	-	-
14 (b)	78	130/95*	Moderate	-	-
16	84	210/140	Considerable	N	-
24	46	160/100	Moderate	N	-

* Higher pressure obtained during stay in hospital.

† + duration greater than normal, —, duration less than normal, N, normal duration.

all the total systoles (ordinates) plotted according to the respective cycle lengths (abscissae). The solid line is drawn to show the normal average—illustrating the theoretical relation between cycle length and total systole ($S = 31 \sqrt{C}$). It will be seen that with the shorter cycles (above the rate of 85) systole falls below the average normal, while with longer cycles (below the rate of 85) systole tends to be slightly longer than the average normal. Cardiac failure is the only factor which we have found to alter the duration of cardiac systole consistently.

In Table 2, the cases are tabulated according to the degree of cardiac failure present. One notes that of the eleven cases without failure,

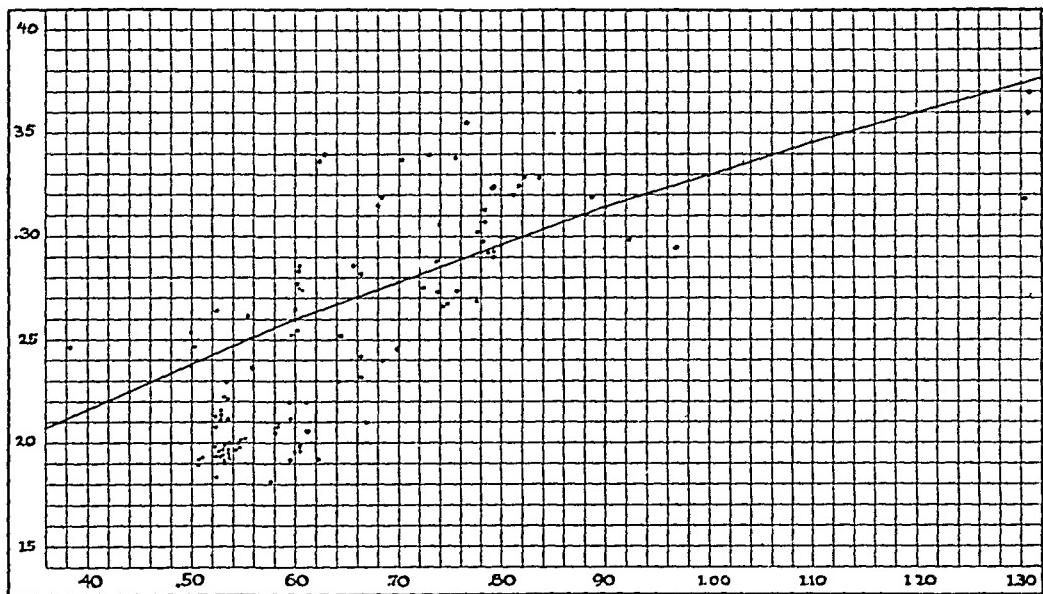


Fig 2.—Plotting of all systoles (total). Ordinates indicate duration of systole, abscissae, cycle length. The solid line drawn to show the normal average illustrates the usual relation between cycle length and total systole. The Katz modification of Lombard and Cope's formula was used in plotting this line ($S = \sqrt{0.31} C$)

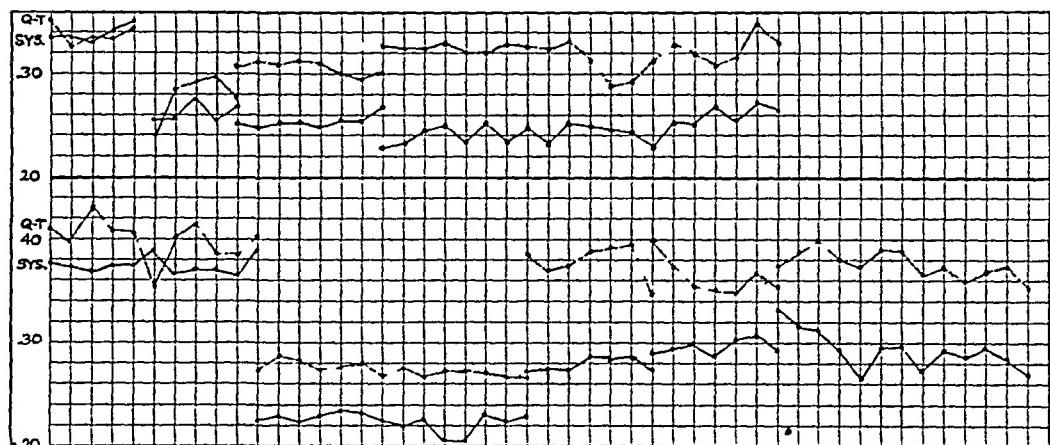


Fig 3.—The directional agreement of the two methods of measuring ventricular systole in nine patients. The interrupted line shows the variations in systole as determined from the electrocardiogram in successive beats. The solid line indicates the systole estimated from simultaneous subclavian and heart sound records

four have a relatively increased duration of systole (Column 5), while the other seven have a normal length. Of the four cases with slight failure, two are of normal duration, one relatively decreased and one relatively increased. Of the nine cases with failure, four have a normal duration, four a relatively reduced duration, and one case has a reduction on one occasion and is normal on another. A failing heart seems to cause an abbreviation of both total systole and the ejection phase.

The relative shortening of the ejection phase in most of these cases occurs more frequently than the reduction in total systole, owing to the prolongation of the isometric period. In other words, the relative abbreviation of ejection in some cases occurs with a normal total systole because the isometric phase is prolonged.

THE VALUE OF Q-R-S-T INTERVAL AS A CRITERION OF VENTRICULAR SYSTOLE

In nine cases, simultaneous electrocardiograms (Lead II) were made with the records of the subclavian pulse and the heart sounds. Although systole as determined by the electrocardiogram exceeded purely mechanical systole by from 0.02 to 0.08 of a second, the directional changes in systole as inscribed by the two methods were usually the same. This relationship is much closer than might be expected from animal experiments (Bartos and Burstein).⁶

COMMENT

The duration of total systole was lengthened in one third of our patients with hypertension, without signs of cardiac failure, whereas in patients with cardiac failure, systole was abbreviated in 50 per cent. The frequent association of shortening of systole in cases of hypertension dominated by failure of the circulation becomes all the more significant when our previous observations are noted, namely, that the abbreviation of systole in auricular fibrillation was greatest when cardiac failure was present. These findings are directly opposed to the results anticipated on the basis of animal experiments. The cause of this apparent discrepancy in cases of cardiac failure is probably due to the fact that our data were obtained from patients having either hypertrophied or incompetent hearts, and it is not surprising that such hearts react differently from hearts of normal animals, from which the experimental data were obtained.

CONCLUSIONS

In the study of twenty-four patients with hypertension we find dynamic changes in ventricular contraction as follows:

1. (a) *Patients without signs of cardiac failure*. Total systole was found to be increased in duration in one third of our cases (by 0.02

to 0.1 of a second) In the other two thirds there was little or no variation from the normal figure

1 (b) *Patients with signs of cardiac failure* Total systole was shortened in one half of the cases (by 0.01 to 0.08 of a second)—in the others, it varied little from the normal average

2 The abbreviation of systole in the cases with failure, we believe, may be due to an altered response of the heart muscle to overloading. On the other hand when it shows no signs of failure its dynamic reaction (lengthening of systole) is shown to be due to the prolongation of the isometric period while the ejection phase either remains normal or is somewhat abbreviated—results anticipated from experimental data

SARCOMA AND CARCINOMA OF THE LIVER FOLLOWING CIRRHOSIS

RICHARD H JAFFE, MD
CHICAGO

The important rôle which chronic irritations play in the etiology of malign neoplasms has been proved by numerous clinical and experimental observations. The facts are too well known to be reviewed, and I will confine myself in the present paper to the reports which deal with the primary malign tumors of the liver and their relations to chronic alterations apparently preceding their development in this organ.

It is an interesting fact that in the liver, which possesses the greatest ability to regenerate, primary malignant tumors are rare. These consist of epithelial tumors derived from the liver cells or epithelial cells of the bile ducts, and mesenchymatous tumors originating either in the stroma or in the endothelium of the blood capillaries. The epithelial tumors are comparatively more frequent than the mesenchymatous ones.

CARCINOMA OF THE LIVER

In the statistics of necropsy material, primary carcinoma of the liver occurs in from 0.02 to 0.3 per cent of the necropsies (Goldzieher and Bokey,¹ Wheeler, Winternitz²) Their percentage of all cancers varies from 1.5 to 3.

The frequent combination of primary carcinoma of the liver with cirrhosis has long been known, indeed it is mentioned in the works of Hanot and Sabourin.³ Liver cell cancers, particularly, are associated with cirrhosis (from 75 to 100 per cent), while for biliary tumors the coincidence is about 50 per cent (Yamagiwa⁴). The causal relation is, therefore, striking, and even since the time of Sabourin has been discussed in almost every publication dealing with cancer of the liver. Ewing,⁵ Winternitz and many other observers are inclined to regard the cirrhosis as a factor predisposing to the formation of the carcinomas.

The objections raised against this assumption are twofold. (a) The combinations may have been a mere coincidence (Kelsh and Keiner) (b) The cirrhotic change assumed to precede carcinoma may, on the

*From the Department of Pathology and Bacteriology, University of Illinois, College of Medicine, and the Uihlein Memorial Laboratory of the Grant Hospital, Chicago.

1 Goldzieher and Bokey Virchows Arch f path Anat **203** 75, 1911

2 Winternitz Johns Hopkins Hosp Rep **17** 142, 1916

3 Sabourin These, Paris, 1881

4 Yamagiwa Virchows Arch f path Anat **206** 437, 1911

5 Ewing Neoplastic Diseases, Philadelphia, W B Saunders Company,

contrary, be a consequence (Markwald,⁶ Wegelin⁷) The great number of observations that have been reported rule out the first contention, but it is admittedly difficult to decide exactly what changes were present in the liver before the cancer started Did the carcinoma cause the cirrhosis by direct injury to the liver tissue or by alteration of the circulation (Markwald,⁶ Wegelin⁷)? The history of the case will, undoubtedly, yield some information The determination of the presumable age of both lesions is important, and the anatomic character of the cirrhotic changes will facilitate the decision Little cirrhosis and fully developed carcinoma speak against a predisposing influence of the former (for example, the case of F Helvestine⁸) Of great value are observations on beginning carcinoma in cirrhotic livers (Saltykow⁹) They may distinctly show how the regeneration of liver tissue due to the cirrhosis exceeds the limits of reparation and, escaping the regulatory influence of the organism, change to an excessive and, finally, carcinomatous growth

The frequency of cirrhosis in cases of primary carcinoma of the liver should not only be considered, but the frequency of carcinomatous degeneration in cirrhotic livers as well Less is known about the latter phase, in future statistics dealing with primary carcinoma of the liver more attention should be given it

In a recent report, Blumenau¹⁰ reviewed the cause of death in 198 cases of cirrhosis of the liver (0.5 per cent of all necropsies) He found that primary carcinoma of the liver had occurred in 35 per cent of them Based on this relatively small statistical material, it may be said that primary cancer of the liver is ten times more frequent in persons suffering with cirrhosis of the liver than in those with other lesions

Guyders and Straub recently reported that primary carcinoma of the liver occurs frequently among the Japanese and Chinese in cases of cirrhosis Appel,¹¹ in six carcinomas in natives of Kamerun, found primary tumors located in the liver four times Cirrhosis was present in each of these cases, and the author discussed the importance of parasitic infections of the liver in this connection Pirie¹² has also mentioned cirrhosis as a predisposing factor in the numerous primary cancers of the liver in the natives of South Africa Several authors

6 Markwald Virchows Arch f path Anat **144** 29, 1896

7 Wegelin Virchows Arch f path Anat **179** 91, 1905

8 Helvestine J Cancer Res **3** 275, 1918

9 Saltykow Sarcoma and Carcinoma of Liver, Cor Bl f schweiz Aerzte **44** 385, 1914

10 Blumenau Arch f Verdauungskrankh **27** 1, 1920

11 Appel Arch f Schiffs-und Tropenhygiene **29** 309, 1921

12 Pirie M J South Africa **17** 87, 1921

(Bamberg,¹³ Loehlein,¹⁴ Necke,¹⁵ Modena¹⁶ Dippelt¹⁷) have found cancer of the liver associated with echinococcus

In the majority of cases observed in this country and in Europe, the cirrhosis associated with carcinoma represented the anatomic type of the atrophic or annular cirrhosis (so-called alcoholic cirrhosis) Some authors found the preceding cirrhosis to be syphilitic in origin (Yamagiwa¹⁸)

In animals, primary tumors of the liver seem to be rare Carcinoma of the liver has been observed in cows, almost invariably connected with severe parasitic biliary cirrhosis (Delafield and Prudden¹⁹)

In material from ten thousand mice of all ages Slye, Holmes and Wells¹⁹ found twenty-eight primary tumors of the liver All were liver cell adenomas, three showing malignant structure, none of which were associated with cirrhotic changes According to the authors, the mouse liver does not show cirrhosis A questionable adenocarcinoma of the liver in a mouse was reported by Shigemitsu Itami²⁰

SARCOMA OF THE LIVER

Approximately forty-eight true primary sarcomas of the liver have been reported to date To the list given by Terplan²¹ should be added the cases of Hektoen,²² Rolleston and Trevor,²³ Hedren,²⁴ Dubs,²⁵ Morrow and McKinstry²⁶ and Goldstein²⁷

Some of the tumors reported as primary sarcoma of the liver must be excluded because they were either not sarcoma or not primary sarcoma of the liver The round cell tumors of the liver associated with similar tumors of the suprarenals and observed only in early childhood are, according to recent investigations, not sarcoma but epithelial tumors derived from indifferent sympathetic nerve cells (neuroblastoma) (Landau's²⁸ bibliography) Whether primary melan-

13 Bamberg, quoted by Winternitz, Footnote 2

14 Loehlein Verhandl d deutsch path Gesellsch **13** 320, 1909

15 Necke, quoted by Winternitz, Footnote 2

16 Modena Pathologica **6** 833, 1913

17 Dippelt, quoted by Winternitz, Footnote 2

18 Delafield and Prudden Text Book of Pathology, Ed 12, Ann Arbor, Mich, George Wahr

19 Slye, Holmes and Wells J M Res **33** 171, 1915

20 Itami, Shigemitsu J Cancer Res **3** 275, 1918

21 Terplan Centralbl f path Anat **31** 453, 1920

22 Hektoen Trans Chicago Path Soc **2** 137, 1896-1897

23 Rolleston and Trevor J Path & Bacteriol **15** 247, 1911

24 Hedren, quoted by Saltykow, Footnote 2

25 Dubs Deutsch Ztschr f Chir **138** 1, 1917

26 Morrow and McKinstry Brit M J **2** 378, 1919

27 Goldstein Internat Clin **2** 73, 1921

28 Landau Frankfurter Ztschr f Path **2** 26, 1912

sarcoma of the liver exists is at least doubtful. The cases without complete necropsy cannot be accepted (F R Hager²⁹ and others)

What are the relations of the primary sarcomas of the liver to cirrhosis? Rolleston and Trevoi, describing an angiosarcoma in a cirrhotic liver, said "Primary sarcoma of the liver is far from common, and when associated with cirrhosis, is distinctly rare." They found six cases in the literature which represented sarcomas in cirrhotic livers. Since their article appeared, seven more cases have been reported (Loehlein,³⁴ Kothny,^{29a} Hachfeld,³⁰ Kahle,³¹ Hedren,³⁴ Saltykow³². Thus 29 per cent of the known cases of sarcoma of the liver were combined with cirrhosis.

Several authors express the opinion that the cirrhosis may have played a predisposing rôle in the formation of the sarcoma (Rolleston and Trevoi,²³ Kahle³¹)

Hedren's spindle cell sarcoma was located in a liver with syphilitic cirrhosis. The cases of Goldstein,²⁷ Dubs²⁵ and de Vecchi³³ are of interest in this connection. Goldstein reported a spindle cell sarcoma in the liver of a man 38 years of age, arising from the wall of a chronic abscess. Dubs reported the case of a girl 26 years of age, who died six months after an injury to the liver. He found a primary spindle cell sarcoma of the liver, 30 by 30 by 25 cm in diameter, and he discussed the possibility of a relationship between trauma and sarcoma. De Vecchi saw a similar tumor derived from the wall of an echinococcus cyst.

The experimental work of Bullock and Rohdenberg,³⁴ and Bullock and Curtis³⁵ proved the possibility of producing sarcomas in the liver in rats by infection with the eggs of *Taenia crassicornis*. But connective tissue of rats seems to be much more apt to undergo sarcomatous transformation than that of human beings.

The hemangio-endothelioma of the liver is derived from the endothelial cells of the capillary vessels of the vena portae. I have previously mentioned that this tumor was sometimes found in cirrhotic livers (Kahle, bibliography, E Schlesinger³⁶)

29 Hager, F R The Surgical Clinics of Chicago **3** 121, 1919

29a Kothny Frankfurter Ztschr f Path **10** 20, 1912

30 Hachfeld Inaugural Dissertation, Halle, 1914

31 Kahle Virchows Arch f path Anat **226** 44, 1919

32 Saltykow Beginning Carcinoma of Liver, Verhandl d deutsch path Gesellsch **15** 292, 1912

33 De Vecchi Soc Med Chir di Bologna **6**, June, 1908

34 Bullock and Rohdenberg J M Res **28** 477, 1913, Rohdenberg and Bullock J Cancer Res **1** 81, 1916

35 Bullock and Curtis Proc New York Path Soc **20** 149, 1920

36 Schlesinger Inaugural Dissertation, Frankfurt, 1920

SARCOCARCINOMA OF THE LIVER AND SARCOMA AND CARCINOMA
IN THE SAME LIVER

There remain sarcocarcinoma of the liver and the separate formation of carcinoma and sarcoma in the same liver. Reports of sarcocarcinoma were published by Lubarsch³⁷ and Saltykow. Both tumors were found in cirrhotic livers.

Of great interest are the rare observations of two different malignant tumors—of a sarcoma and of a carcinoma—in different parts of the same liver. I am aware of but two cases so far reported.

The first case is that of Dominici and Merle³⁸. A man, aged 56, died a short time after his admittance to the l'Hotel-Dieu in Paris. Alcoholism was mentioned in his history. The liver showed a definite atrophic cirrhosis and was interlaced by tumor masses. There were metastases in the lower lobe of the right lung, in the head of the pancreas and in the suprarenals. Microscopic examination revealed old cirrhotic changes in the liver. There was adenomatous hyperplasia of the liver tissue, which passed over directly to carcinomatous areas. In these places the liver cells had lost their structure entirely and appeared as small cells of embryologic character. In a part of the liver with less cirrhosis a spindle cell sarcoma was detected. The metastases were formed by sarcomatous tissue.

The authors conclude their observation with the remark "Ce cas anatomo-pathologique est un des exemples les plus typiques que l'on puisse trouver d'association entre les processus de tumeur et des processus d'inflammation chronique."

The other case was observed by Saltykow. The patient was a man aged 62. Nothing is reported about the history. At necropsy two tumors were found besides distinct atrophic cirrhosis. The larger tumor, 20 by 16 by 9 cm in size, was a typical spindle cell sarcoma, the smaller tumor, 3 cm in diameter, was an early liver cell carcinoma.

To these two cases I wish to add a third.

REPORT OF A CASE

History—A white man, aged 64, a traveling salesman, said he did not have a chancre. He had had gonorrhea several times years ago. He had been a hard drinker in former years. The clinical diagnosis of cirrhosis of the liver was first made fifteen years ago. About three months before admittance to the hospital the patient had had dull pains in the epigastrium and belching of gas. He had no appetite, was usually constipated and the stools had an offensive odor. When the patient was brought to the hospital, he seemed to be rather dull, and he was not responsive to questions. He passed only a few drops of an almost black urine. He died two days later.

37 Lubarsch Zur Lehre von den Geschwulsten, 1899

38 Dominici and Merle Arch de med exper et d'anat path 21 136, 1909

Necropsy (Sixteen hours after death)—The body was that of a fairly well nourished man, 175 cm long. The skin and eyeballs were distinctly yellow. The abdomen was distended.

The situs of the abdominal organs was normal. The bladder was empty. The lungs were voluminous, their edges appeared rounded. The lung tissue in all parts was of normal air content and hyperemic.

The heart was of normal size, covered partly with fat tissue, and very loose. In its cavities were postmortem blood clots. The myocardium was grayish brown and friable. The endocardium over the papillary muscles was thickened. The valves were unaltered. There were little calcified plaques in the ascending part of the aorta.

The liver was covered partly by the adherent omentum and firmly attached to the diaphragm. Its form was very irregular. The right lobe was almost entirely replaced by a spherical mass, 17 by 12 by 14 cm in size. On the



Fig 1.—Cross section through the liver, 1, sarcoma, 2, carcinoma

surface not covered by the diaphragm larger and smaller nodes of white or reddish white color were prominent. The left lobe was small, and its surface showed small, flat, grayish brown nodules with lighter strips between them. There was a single larger node softer and more yellowish in color.

Cross sections (Fig 1) through the liver showed that the right lobe consisted of a dense and faintly reddish stained tissue. Wavy bands of reddish white alternated with more grayish ones. This tissue continued into the muscles of the diaphragm as tortuous bands. The center of the lobe was formed by an irregular cavity filled with a thick reddish gray, cheesy material. There was little liver tissue left around the dense masses.

The left lobe revealed, on the cut surface, a mosaic-like structure. Round, grayish brown nodules were separated by firm, grayish white bands. The diameters of the soft yellow nodule mentioned above were 2 by 1 cm. It was located just below the capsule and was formed by a homogeneous tissue

(Fig 2) Adjacent to it several smaller oval areas of a similar appearance could be observed. The wall of the gallbladder was partly replaced by white or grayish white nodules which bulged into the cavity. The mucosa was yellow and ulcerated over the nodules. A yellowish gray mucus filled the cavity. There were no calculi.

The vena portae and its branches seemed to be free, as did also the arteria hepatica and the vena hepatica. There was no enlargement of the lymph glands.

The spleen was somewhat enlarged, its weight was about 200 gm. Its capsule showed singular thickened areas. The pulp was red and soft, but the structure was distinct.

The suprarenals were colliquated and changed to a brown and pulpy mass.

The kidneys were embedded in fat tissue. Their surface showed small cysts, in the left kidney there was a larger cyst, 3 cm in diameter. The kidneys were dark grayish red, and in the medulla, small glittering, whitish stripes were noted.

In the colon were claylike masses. The blood vessels of the mucosa of the stomach were somewhat dilated.

Microscopic Examination—Left Lobe of the Liver. Round and oval islands of liver tissue varying in size from the fourth of a normal acinus to its twofold or threefold diameter were surrounded by connective tissue. In these islands, the normal structure of the acini was gone. The central vena was distorted and some acini had two or three central venae. The columns of the liver cells ran in various directions without distinct arrangement around a central blood vessel. The majority of the liver cells themselves were more or less altered. Many of them were smaller than normal, their nuclei were poorly stained or they were shrunken and dark. The cytoplasm contained yellow-brown granules of iron-free pigment. Many cells showed smaller or larger fat droplets, some cells were filled with fat which stained yellowish red with Sudan III and pink with Nile-blue sulphate. At the periphery of the acini, where proliferating connective tissue invaded the acini, single liver cells became isolated and showed extreme fatty degeneration. The fat gave double refraction and stained violet with Nile-blue sulphate.

Between the degenerated and atrophic liver cells, larger and well preserved cells were intercalated. Their protoplasm was homogeneous, and their nuclei had a distinct chromatin network with a round nucleolus. Cells with two nuclei were frequent. Sometimes the nuclei were large and irregular. Their edges were notched and their chromatin formed clumpy, dark masses.

In some places within the areas of the liver cells, an increased amount of connective tissue was present. Using Mallory's stain and silver impregnation, it was found that these fibers were derived from the thickened and clotted reticular fibrils.

The septums separating the areas of liver tissue were from 0.5 to 2 cm in thickness. They were formed by dense fibrous tissue with a few small and dark nuclei. A larger number of cells occurred in those parts of the fibrous tissue in which the bile ducts proliferated. Sometimes the proliferation of the bile ducts was so pronounced that adenoma-like formations resulted. There were areas, 1.5 mm in diameter, consisting almost entirely of larger and smaller bile ducts. A circumscribed increase of cells was also formed by accumulations of round cells. They were located at the periphery of the septums and often infiltrated the adjacent liver tissue. Here the liver cells, as described above, underwent intensive fatty degeneration, and itinerant cells with fat granules joined the lymphocytes of the infiltrates.

The subcapsular soft node of the left lobe was formed by a tissue very irregular in arrangement and of cells that resembled liver tissue (Fig 2). There were rows of cells lining capillary vessels with a distinct endothelium. The cells were small, cuboid, packed closely together, with very dark and wrinkled nuclei. In the same rows there were large polyhedral cells. The nuclei of these cells were partly round and showed a chromatin structure like

that in the nuclei of normal liver cells. Often the nuclei were extremely enlarged and deeply stained. Vacuoles distended them so that peculiar forms resulted.

There were parts wholly formed by the latter type of cells. The cells contained droplets of yellowish brown, iron-free pigment. It was located either in single, small vacuoles or it filled the whole body of the cell. Some cells showed a diffuse brownish color. The pigment continued as small stripes connecting the masses within the cells with homogeneous, pigmented material between them.

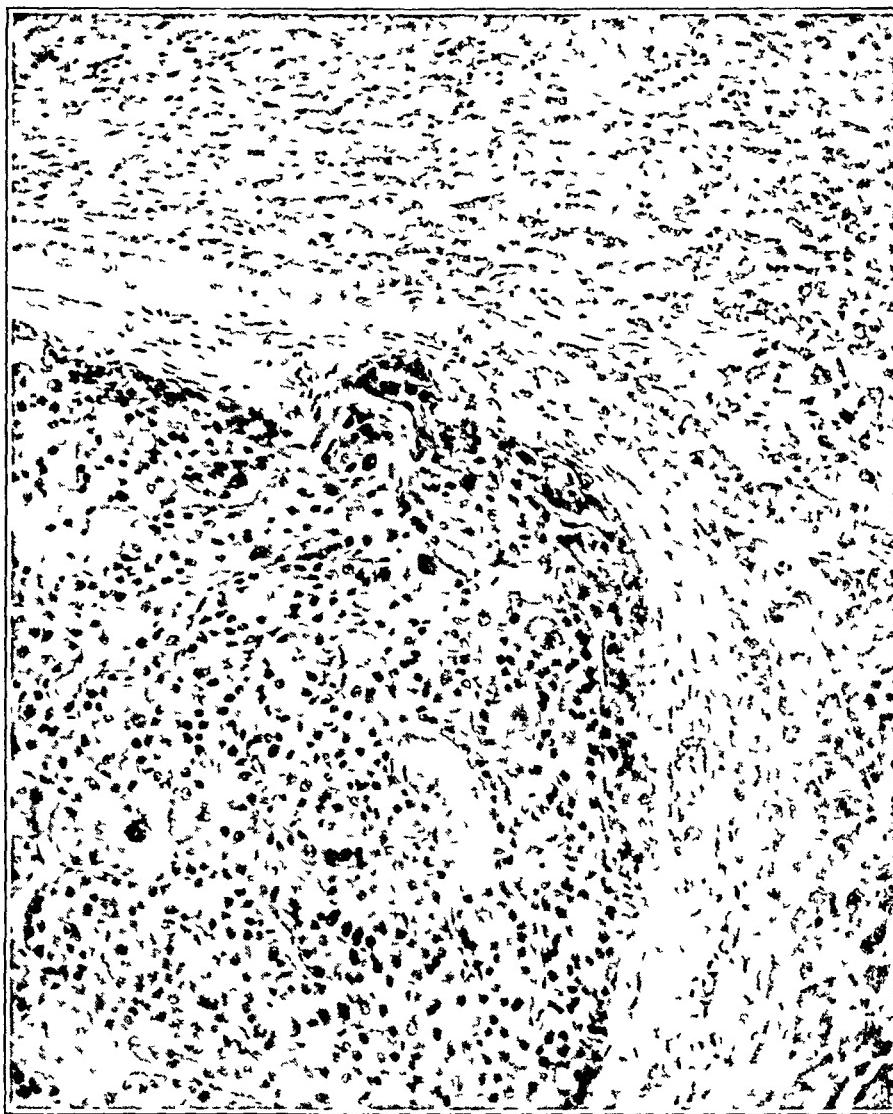


Fig. 2.—Liver cell carcinoma, tumor mass in a branch of the vena hepatica.

This pigment differed from the normal bile pigment in its consistency, being apparently more fluid, and in color paler and more yellowish. Stained with Malloy's phosphoric-molybdic hematoxylin, the normal bile appeared dark green or brown-green, while the pigment of the irregular parts took up only a pale yellowish green. The atypical liver cells appeared to have produced an atypical secretion.

Mitotic figures were rare. The proliferation of the cells seemed to be the result of amitotic division as indicated by the various stages of constriction of the nuclei.

Silvei impregnation (Bielschowsky-Maresch) revealed a loose and irregular reticulum between the cells.

The center of the nodes was necrotic and contained no nuclei. Droplets of neutral fat and coarse granules of dark yellow pigment filled the necrotic cells, disintegration often occurred so that the fat and pigment became free. Besides these masses the debris contained needles of fatty acids and double refracting fat. The atypical liver tissue was not connected directly with the other parts less irregular in their structure. A small amount of fibrous tissue separated them from each other. In the vicinity of the node smaller areas of atypical

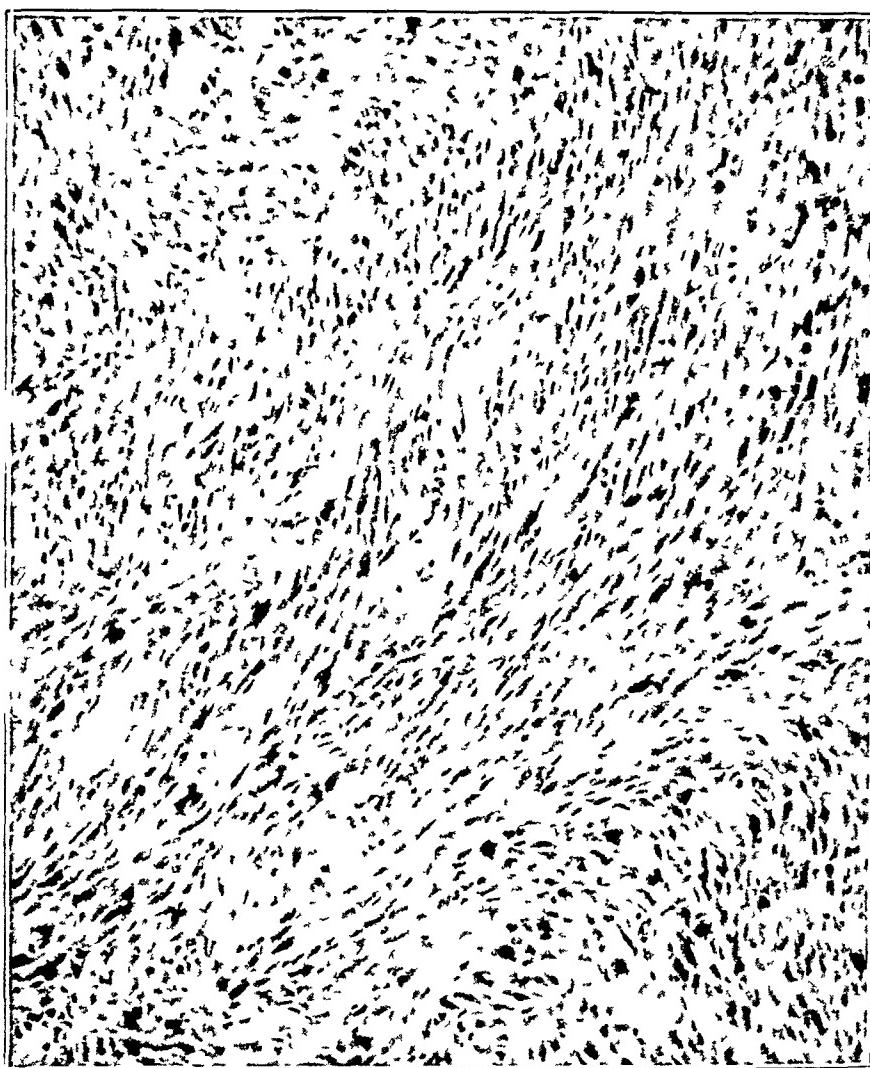


Fig 3.—Spindle cell sarcoma

cells were found. They were located within blood vessels as the well preserved wall of the vessels at their periphery still indicated. Sometimes the lumen of a vessel was not closed up by the cell masses, the latter being separated from the endothelium of the wall by a layer of clotted blood.

The microscopic structure of the large tumor of the right lobe of the liver could be recognized at the periphery, the central parts being necrotic. There the tumor was composed of large fusiform cells, from 70 to 100 microns in length (Fig 3), forming bundles which interlaced in various directions. The majority of the nuclei were spindle shaped and dark, with a dense chromatin meshwork

Some nuclei were larger and more irregular. They were bent, kidney-like or horseshoe-like, or they were segmented and tortuous. Between the fusiform cells single cells were conspicuous because of their great size and their dark nuclei.

Mitotic figures of the nuclei were frequent, in every field of the higher power magnification two or three of them could be found. Their forms were often atypical with asymmetric arrangement of the chromosomes, three or four poles, etc.

Fatty Changes.—A peculiar feature of the tumor was the result of fatty changes. All the cells contained fat droplets, even those with mitoses. Some cells had only a few small droplets; in other cells the body was filled up with fat. If the nucleus was just undergoing mitotic division, the droplets were located at the periphery of the cells in a regular wreath. In some, the fat was mixed with the chromosomes.

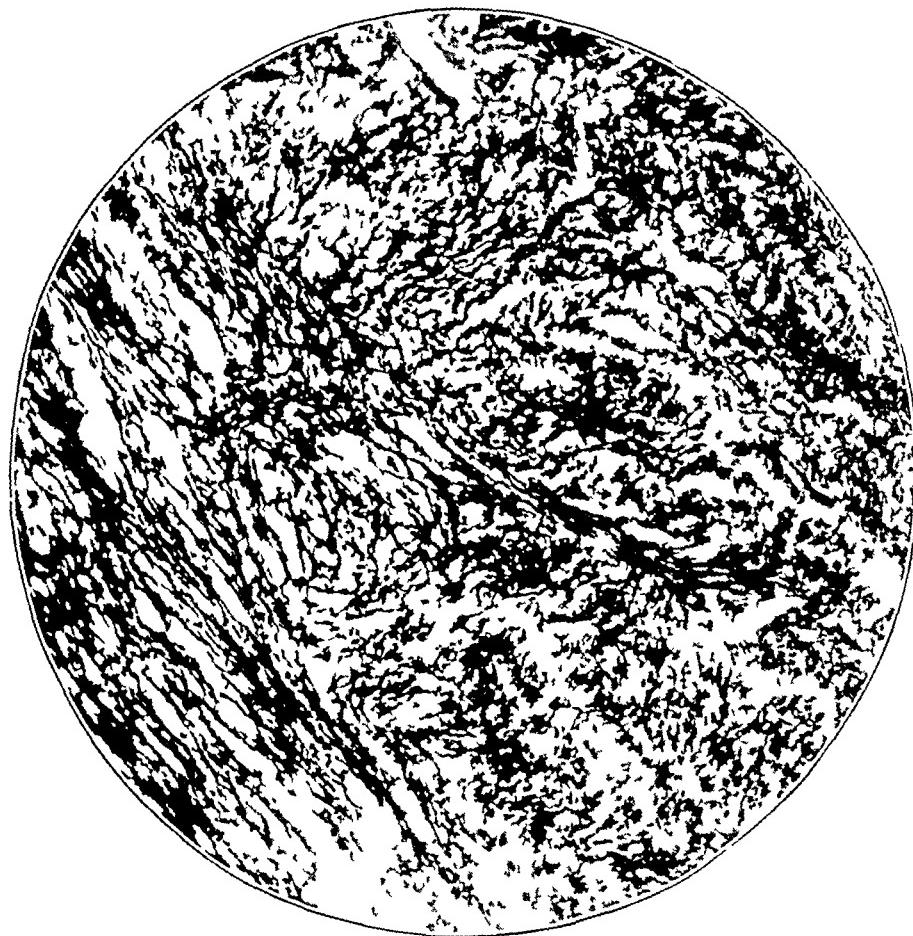


Fig. 4.—Spindle cell sarcoma, Bielschowsky's stain

The fat stained yellowish red or orange with Sudan III. With Nile-blue sulphate, the larger droplets took up a purple color and were often surrounded by dark blue rings or dark blue granules. The droplets of medium size were violet and the small fat granules were dark blue. Fischler's microreaction for fatty acids was positive in some of the larger droplets. The membranes and granules around the larger droplets stained blue with Nile-blue sulphate and gave a black impregnation with Lorrain-Smith chromehematoxylin. Only the small droplets showed double refraction. In the necrotic parts all fat was stained pink with Nile-blue sulphate. The Lorrain-Smith impregnation was negative. There was no double refraction.

According to these findings, it can be said that the larger droplets are formed by neutral fat which often contains free fatty acids. The droplets are

surrounded by membranes of a complicated lipoid mixture. In the small droplets, cholesterol esters are present. In the necrosis, all fat is neutral fat.

Connective Tissue.—In the sections stained with hematoxylin and eosin or with van Gieson's picric acid, acid-fuchsin solution, little collagenous tissue could be seen between the fusiform cells. Using Mallory's stain for connective tissue or Bielschowsky's and Maresch's silver impregnation, the large amount of fibers which surrounded and separated the cells was astonishing (Fig. 4).

A basket-like network was formed above the cells by brushlike branches given off from the side of thicker longitudinal fibers. Toward the central parts where the tumor cells became necrotic the network of fibers was intact, it seemed even to be denser because the fibers were more closely packed together. Only near the central cavity did the fibers break up into granules and irregular segments.

The relation of the tumor to the connective tissue of the cirrhotic part. The tumor was directly connected with the cirrhotic connective tissue. The transition zone between them was rather sharp, only at a few points did the large spindle cells invade more deeply the tissue of the septums. Where the tumor bordered on liver tissue, liver cells became isolated by the tumor just as they were by the fibrous tissue of the cirrhosis. The liver cells located within the tumor were greatly altered, showing fatty degeneration, atrophy and necrosis. The framework of the old acini could still be recognized in the midst of the tumor.

The nodes in the wall of the gallbladder showed the same structure as the tumor in the right lobe of the liver. They contained large spindle cells arranged in bundles, with dark nuclei, often atypical. In some parts a considerable amount of connective tissue was elaborated by these cells. Inside the gallbladder the tumor was necrotic and stained by bile pigment. On the outside, the muscle fibers were still present, although disintegrated and compressed by the invading tumor cells.

Kidney. Few glomeruli were obliterated in the kidney. In the epithelial cells of the convoluted and straight tubules, droplets of neutral fat were found. The cyst was lined with flat epithelium and filled with homogeneous masses. There was little sclerosis in the larger arteries.

The glittering stripes in the medulla were formed by thickened and hyaline interstitial tissue. They contained groups of fat droplets. On microchemical examination it was found that the fat consisted of neutral fat, fatty acids and lime soaps.

Spleen. The malpighian bodies were small. In the pulp the reticulum was distinctly thickened. The sinuses were filled with blood. There were few lymphoid cells and plasma cells besides the erythrocytes.

Microscopic examination of the other organs revealed no important changes.

COMMENT AND SUMMARY

In the present case the clinical diagnosis of cirrhosis of the liver was made fifteen years ago. In accordance with this, the anatomic examination revealed an extensive transformation of the liver. That the cirrhosis was still progressing was indicated by the recent changes on the periphery of the acini.

The tumor in the right lobe of the liver was a typical spindle cell sarcoma. It originated in the fibrous septums between the transformed acini. It seems that the slowly progressing new formation of connective tissue had suddenly taken on an extremely rapid and destructive proliferation, the cells showing a tendency of growing around the liver acini and imitating the periacinar growth of the cirrhotic connective tissue from which they were derived.

The spindle cells of the tumor were connected by a well developed meshwork of reticular fibers, formed, no doubt, by the tumor cells themselves. Hatuso Kuru³⁹ considers such a reticular network typical of the spindle cell sarcomas.

It is, of course, not possible to determine exactly the date when the sarcoma started. But the rapid progress of the disease during the last month of life and the great number of mitotic figures indicate that the tumor grew fast.

Primary sarcomas of the liver are not apt to produce metastases. In this case, metastases occurred only in the gallbladder. There is no doubt that the tumors of the gallbladder were secondary to the tumor in the right lobe of the liver. In a previous paper,⁴⁰ I have described the differences between primary and metastatic sarcoma of the gallbladder.

In the liver cells marked degeneration was observed which apparently had developed shortly before death. There were areas of liver cells which were free from degenerative changes, these were the zones of regeneration. In one area in the left lobe, the new formation of liver tissue had exceeded the limits of regeneration. Here the cells showed all the signs of a destructive and malignant proliferation. At the periphery the cells were small with relatively large and very dark nuclei (embryologic, Dominici and Merle³⁸). Toward the center the cells became large and atypical, although they still resembled liver cells. They were arranged along capillary blood vessels and manifested an attempt at bile formation. They had invaded hepatic veins and spread out within their lumen. Because of these findings the tumor in the left lobe of the liver is called a liver-cell carcinoma (hepatoma).

It is a question whether the single atypical cells found in other parts of the liver in close connection with regenerative changes may be regarded as further centers of beginning carcinomatous growth. That would indicate a multiple origin of carcinoma. These cells were certainly not metastatic tumor cells, for they were located within the columns of the liver cells and not between them in the capillaries.

We know that atypical cells are not rare in regenerative tissue growth, and one is not justified in making a diagnosis of beginning carcinoma from a single cell. I suppose that the irregular cells in certain areas resulted from the efforts of an extensive regeneration. While the boundless destructive proliferation of the cells appeared in various parts, only in one place did it lead to the formation of a true carcinoma.

39 Kuru Verhandl d deutsch path Gesellsch **13** 386, 1909

40 Jaffe Centralbl f path Anat **29** 571, 1918

From the clinical history and the result of the microscopic examination, we believe that in the present case the cirrhosis preceded the carcinoma as well as the sarcoma. Both tumors had developed from tissue which can be identified as of cirrhotic origin.

The connective tissue between the transformed liver areas was old scar tissue. That sarcoma may arise from scar tissue is well known (Simon¹¹), and it is interesting that the majority of these sarcomas are of the spindle cell type. The cirrhosis may be regarded as having favored the formation of the sarcoma.

I have stated that the carcinoma started in regenerated liver tissue. The regeneration was due to the cirrhotic destruction of the liver, but it was, no doubt, greatly stimulated by the sarcoma which had destroyed almost the whole right lobe. Some causal relations, therefore, may have existed between the two malignant tumors.

41 Simon Ztschr f Krebsf **10** 210, 1911, Berl klin Wchnschr **3** 1914

ARTERIOSCLEROSIS AND HYPERTENSION ~

JAMES P O'HARE, MD

AND

WILLIAM G WALKER, MD

BOSTON

Some time ago, while making routine examinations of the eyegrounds in the medical wards, a finding of peculiar interest and of great importance was noted. A patient with typical advanced arteriosclerosis of the radial and brachial arteries had absolutely normal retinal vessels. It was assumed at the time that this was merely an accidental finding. Later, however, we observed the same phenomenon in another patient. Analyses of these two cases disclosed the fact that both patients had normal blood pressures. Among the more recent references to retinitis of circulatory disease are those of Schieck and Volhard,¹ Benedict,² Behan³ and Cohen.⁴ For the most part, these are descriptive of the lesions found in the retina, together with speculations on cause and effect. We were cognizant, of course, from Allbutt's writings and our own experience, that marked peripheral arteriosclerosis could occur with normal blood pressure. We were unaware, however, of any published observations on the retinal vessels in such cases. Practically the only reference to the relation between blood pressure and large and small vessel sclerosis is an indirect one by Moore,⁵ who found that in twenty-one patients suffering from intrathoracic aneurysms, with an average systolic pressure of 141 mm. "There was no evidence of any considerable disease of the retinal arteries in any case." The same author states that hypertension is the rule when retinal arteriosclerosis is present. It was felt that if our observations could be verified in a large series of cases, it would throw light on the relation between arteriosclerosis and blood pressure. Consequently, we examined as

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1 Schieck, F., and Volhard, F. Netzhautveränderungen und Nierenleiden, Zentralbl f d ges Ophth 5 465-470, 1921

2 Benedict, W L. Retinitis of Cardiovascular and Renal Diseases, Am J Ophth 4 495-499 (July) 1921, Retinitis of Acute Nephritis, Report of Six Cases, M Clinics N America 5 275-288 (Sept.) 1921

3 Behan, J L. Fundus Changes in Nephritis, J A M A 78 1691-1694 (June 3) 1922

4 Cohen, M. Significance of Pathologic Changes in Fundus in General Arterial and Kidney Diseases, J A M A 78 1694-1701 (June 3) 1922

5 Moore. Medical Ophthalmology, Philadelphia, P Blakiston's Son & Company, 1922

many of these nonhypertensive peripheral sclerotic patients as we could find. To date, these have numbered fifty. In passing, it may be worth mentioning that many of these persons are old, and that cataracts or other opacities in the media are extremely common. This naturally reduces markedly the number of available cases, because the retinas in such cases cannot always be seen with sufficient clarity to pass judgment on the vessels.

It seemed desirable to contrast with these nonhypertension cases a group of patients with peripheral sclerosis who showed hypertension and, if possible, another group of hypertensive patients who did not show peripheral arteriosclerosis. We were not successful in obtaining cases of the latter type, because, while many showed no obvious sclerosis of the radials and brachials, most showed at least slight thickening and tortuosity of the temporals. It was, therefore, decided to include all of these cases in the other group of hypertensive patients. As a rule, the cases in Table 2, in which the patient's peripheral vessels are noted as slightly thickened or tortuous are those in which the obvious sclerosis is confined to the temporal vessels. There has always been a question in our minds about the importance of tortuous temporal arteries. They seem to be common in apparently normal people. In a study of this kind, however, it was deemed necessary to include them.

Our observations on the peripheral vessels were confined to the radials, brachials and temporals. No doubt, additional information might have been obtained from examination of the arteries in the legs. But for our purposes the examination of the three mentioned seemed sufficient.

In the examination of the retinal arteries, we confined ourselves largely to the two signs of arteriosclerosis that are absolute and beyond criticism. These signs are compression effects at arteriovenous crossings and irregularity of the lumen. We included also with the latter the more advanced signs of sclerosis—beading and obliteration of the red columns through increasing opacity of the wall. We felt that the other signs of sclerosis were too variable and too dependent on personal judgment of what was normal and what was pathologic.

The results of this study are embodied in Tables 1 and 2. Table 3 is a summary of Tables 1 and 2. In the first table are included fifty cases of peripheral arteriosclerosis with systolic blood pressures under 145. The peripheral sclerosis varied from slight tortuosity or thickening to beading and calcification. More than one half of these show at least "marked sclerosis." In contrast, the retinal vessels show almost no sclerosis (This is brought out better in Tables 2 and 3.) From the arrangement of the blood pressures according to an ascending value for the systolic, it can readily be seen that there is no relation between the

height of either the systolic or diastolic pressure and the degree of sclerosis. No comparison, of course, can be made between the pressures and retinal vessel sclerosis in this group—there is so little sclerosis.

The average age in this group is 55.6 years, the extremes being 13 and 82 years. The average is probably lowered considerably by two

TABLE 1—*Types of Sclerosis in Patients with Various Diseases**

Case No.	Age	Diagnosis	Blood Pressure	Peripheral Vessels	Retinal Vessels
1	61	Peptic ulcer	89 / 48	++++	0
2	47	Convalescence from pneumonia	92 / 57	++	0
3	28	Diabetes	92 / 64	++	±
4	60	Aortic insufficiency, chronic nephritis	100 / 40	+++++	±
5	18	Diabetes	101 / 80	++	0
6	65	Chronic bronchitis, arthritis	102 / 50	++++	±
7	46	Diabetes	102 / 71	++	0
8	15	Diabetes	104 / 69	++	0
9	50	Chronic arthritis arteriosclerosis	104 / 70	++	0
10	32	Subacute nephritis	104 / 84	++	0
11	68	Paralysis agitans, cystitis	108 / 54	++	0
12	32	? Chronic nephritis	108 / 68	++	0
13	55	Chronic nephritis	108 / 72	++	0
14	41	Diabetes	108 / 82	+++	0
15	47	Epilepsy	108 / 86	++	0
16	60	Diabetes	110 / 70	+++	±
17	65	Cancer of intestine	110 / 70	+++++	0
18	35	Diabetes	110 / 71	+++	0
19	63	Bronchial asthma, emphysema, myocarditis	112 / 70	+++++	++
20	77	Chronic bronchitis	115 / 60	+	0
21	82	Arteriosclerosis	120 / 60	++++	0
22	77	Chronic myocarditis, auricular fibrillation	120 / 62	++	±
23	77	Convalescence from pneumonia	120 / 70	++++	±
24	31	Acute bronchitis	120 / 84	++	±
25	74	Aortic insufficiency, chronic bronchitis	122 / 50	++++	+
26	54	Chronic nephritis	122 / 68	+++	±
27	73	Chronic myocarditis, chronic nephritis	122 / 71	++	+
28	55	Leukemia	122 / 80	+++	++
29	35	Acute arthritis	122 / 74	++	±
30	42	Asthmatic bronchitis	124 / 108	++	0
31	60	Diabetes	126 / 57	++++	±
32	57	Syphilis	127 / 10	+++	+++ only 1 vessel
33	60	Diabetes	129 / 74	++++	++
34	60	? Cerebral hemorrhage	130 / 80	++++	±
35	69	Arteriosclerosis	130 / 80	+++++	±
36	58	Fezema of leg and ear	130 / 86	+++	++
37	49	Diabetes	130 / 80	+++	0
38	76	Chronic myocarditis	132 / 72	+++	±
39	38	Ovarian cyst, anemia	132 / 82	++	0
40	44	Cystitis and prostatitis	134 / 90	++	0
41	75	Chronic myocarditis	135 / 85	++	±
42	67	Cancer	136 / 66	+++++	+
43	58	Pulmonary tuberculosis	136 / 69	+++++	±
44	54	Tuberculosis ? old hemiplegia	138 / 40	+++++	±
45	67	Chronic myocarditis	138 / 90	++++	0
46	53	Chronic myocarditis	138 / 91	++	±
47	81	Chronic interstitial nephritis	140 / 60	++	±
48	72	Chronic myocarditis	140 / 65	++	±
49	64	Aortitis, aortic stenosis and regurgitation	142 / 28	++	0
50	59	Auricular fibrillation, chronic myocarditis	130 / 82	++++	±

* In the column headed "Peripheral Vessels," + means slight sclerosis, ++, moderate sclerosis, +++, marked sclerosis +++, calcified, and ++++, "beaded." In the column headed "Retinal Vessels," ± means questionable sclerosis, +, slight sclerosis, ++, moderate sclerosis, and +++, marked sclerosis.

very young patients—one 13 and the other 15. Our impression had been that the typical patient in this group was much older than the average patient with hypertension. However, in Table 2, the average age was 53.6 years, only two years less than the average for the first group. The extremes were 23 and 85 years.

In the second table are fifty cases of peripheral sclerosis with systolic pressures over 145. The degree of peripheral sclerosis in this group averages somewhat less, the bulk of the cases being designated "moderate" or less. That these cases may show extensive sclerosis, however, is illustrated by the fact that eleven were classified as "marked" and five as "beaded" or "calcified." The lack of relationship between

TABLE 2.—*Sclerosis in Persons with a Systolic Pressure over 145**

Case No	Age	Diagnosis	Blood Pressure	Peripheral Vessels	Retinal Vessels
1	39	Chronic nephritis	160 / 103	+++	+
2	85	Fractured hip	164 / 80	+++++	±
3	26	Vascular hypertension	166 / 96	+++	++
4	59	Vascular hypertension	170 / 100	++	+++++
5	63	Vascular hypertension	174 / 112	+++++	++++
6	44	Chronic nephritis	178 / 120	++	++++
7	63	Chronic nephritis	180 / 120	++	+++
8	54	Chronic nephritis and myocarditis	184 / 114	+++	++
9	60	Aortic insufficiency, syphilitic aortitis, myocarditis	186 / 78	++++	++
10	51	Diabetes mellitus	188 / 92	++	++
11	58	Hypertension, chronic myocarditis	188 / 112	+++	+++
12	54	Chronic nephritis	189 / 110	++	++
13	71	Hypertrophic arthritis	190 / 90	+	+++
14	52	Chronic nephritis	190 / 100	++	+++
15	61	Auricular fibrillation	190 / 110	++	++
16	63	Chronic nephritis, myocarditis	190 / 112	+++	+++
17	63	Mitral endocarditis, hernia	190 / 120	++	+++
18	48	? Chronic nephritis	190 / 140	+++	+++
19	80	Tubes, necrosis of bone	192 / 80	+++	++
20	26	Chronic nephritis, myocarditis	192 / 120	+++	+++
21	75	Chronic myocarditis	194 / 94	++++	++
22	52	Vascular hypertension	194 / 112	++	++
23	56	Asthma	195 / 112	+	+++
24	62	Cerebral hemorrhage, old	196 / 113	++	+++
25	52	Cerebral hemorrhage	198 / 110	+	+++
26	23	Chronic nephritis	199 / 158	++	++++
27	46	? Chronic myocarditis, ? aortitis	202 / 144	++	+++
28	53	Chronic myocarditis, ? chronic nephritis	205 / 105	++	+++
29	56	Vascular hypertension	208 / 112	++	+++++
30	55	Chronic nephritis	210 / 112	++++	++
31	57	Chronic nephritis, myocarditis	210 / 116	++	+++
32	46	Chronic myocarditis	210 / 130	++	+++++
33	51	Myocarditis	215 / 130	++	++
34	37	Chronic nephritis	216 / 124	++	++
35	48	Chronic myocarditis	216 / 138	++	++++
36	29	Chronic nephritis, myocarditis	216 / 168	+++	+++
37	43	Vascular hypertension	218 / 104	++	+++
38	47	Chronic nephritis	218 / 144	++	++
39	77	Aortic insufficiency, chronic nephritis	220 / 90	+	+++
40	52	Chronic nephritis	200 / 134	+++	++
41	74	Inguinal hernia	222 / 108	++++	+++
42	57	Vascular hypertension, cirrhosis of liver	225 / 104	+	+++
43	57	? Chronic nephritis	232 / 120	+	++
44	57	Vascular hypertension	232 / 130	++	+++
45	47	Chronic nephritis	234 / 105	++	+++
46	45	Chronic nephritis	234 / 160	+	+++++
47	43	Chronic nephritis	240 / 115	++	+++
48	41	Chronic nephritis, myocarditis	242 / 154	++	+++
49	58	Chronic myocarditis, arthritis	254 / 110	±	+++
50	30	Chronic nephritis, myocarditis	266 / 130	++	+++

* Under "Retinal Vessels," ++++ means beading and +++++ indicates vessels represented merely by white lines. Other signs have same meaning as in Table 1.

peripheral and retinal sclerosis is particularly well demonstrated in this table. The patient in Case 2 had radial vessels that were definitely calcified, and yet the retinal vessels showed only questionable pressure effects and unevenness. In contrast is Case 46 in which the radials were only slightly thickened and tortuous, while many of the retinal vessels were so sclerosed that they were represented merely by white

lines. What was said about the lack of relation between blood pressure and peripheral sclerosis is, therefore, confirmed in this group. This lack of relationship extends also to the retinal sclerosis. The last column shows clearly that there is a marked association between hypertension and retinal sclerosis. Closer scrutiny will show that the height of the pressure is independent of the degree of retinal sclerosis. There is a tendency for high diastolic pressures to be associated with the higher degrees of retinal sclerosis, but this is only a tendency. Several cases with high diastolic pressures show only moderate pressure effects and unevenness in these vessels. Furthermore, many of the cases of marked sclerosis are in patients with a relatively low systolic or diastolic pressure. We can hardly expect such a relationship. The blood pressure is so variable and fluctuates so markedly from moment to moment that it is inconceivable that it could be entirely dependent on a factor so fixed as arteriosclerosis of the small blood vessels. The

TABLE 3.—Degree of Sclerosis of Retinal Vessels in Hypertensive and Nonhypertensive Cases

	Hypertensive Group, Percentage	Nonhypertensive Group, Percentage
Normal arteries	0	44
Questionable sclerosis	2	38
Slight sclerosis	2	8
Moderate sclerosis	28	8
Marked sclerosis	52	2
Beaded sclerosis	8	0
"White line"	8	0
	100	100

vasoconstrictor and vasodilator elements as well as the heart are factors which always must be considered.

Although the relationship between the degree of retinal sclerosis and the blood pressure is not a quantitative one, there is no question about a qualitative relationship (Table 3). To us the proof seems absolute.

The contrast between the two groups is indeed extraordinary. Whereas, in the hypertensive patients 68 per cent showed a grade of retinal sclerosis classified as "marked" or even more than that, in the other group, 82 per cent had practically normal vessels and only one case showed "marked" sclerosis. In this patient, moreover, the marked unevenness of caliber was confined to a single vessel.

During our search for persons with low pressure and sclerosis, four cases were discovered which were extremely stimulating and confirmatory of what we have written in the foregoing on the relation between retinal sclerosis and hypertension. These cases are the first four in Table 4. They were presented to us as cases of peripheral sclerosis with normal blood pressure. Without knowing anything more

about the patients, we made an examination of the fundi, and found that two of the patients showed marked sclerosis and two moderate sclerosis. These four cases offer the strongest proof of our thesis. On obtaining the histories of the patients, we discovered that all of them had previously been hypertensive, as indicated in Table 4. We have subsequently added twelve more cases from our records which illustrate the same phenomenon. In only two were the retinal vessels normal. Such facts offer much food for thought. They suggest strongly that although hypertension occasionally occurs without evidence of sclerosis in the retinal vessels, the finding of the latter indicates the probability of a previous hypertension.

TABLE 4.—*Patients with Normal or Low Pressure Who Previously Have Had Hypertension*

Case No	Blood Pressure	Previous Blood Pressure	Retinal Vessels
1	120 / 80	170 / 96	+++
2	134 / 65	162 / 72	++
3	144 / 72	160 / 80	++
4	147 / 85	210 / 100	
5	108 / 72	208 / 100	+++
6	128 / 68	200 / 100	+
7	130 / 82	240 / 102	++
8	132 / 112	199 / 158	++++
9	140 / 80	270 / 190	++
10	142 / 28	180 / 35	0
11	142 / 80	192 / 100	+
12	142 / 86	180 / 120	+
13	142 / 88	180 / 90	++
14	144 / 94	190 / 100	+
15	148 / 87	172 / 84	+
16	150 / 68	185 / 90	++++

To us, these observations, even in a small series of 100 cases, are of special importance. First, they emphasize the great importance of examining carefully the retinal vessels instead of merely glancing at the fundi for the far less important hemorrhages and white spots. It has been shown definitely by Moore⁶ that the condition of the retinal arteries is a close guide to the condition of the cerebral vessels. Consequently, they must be of considerable prognostic value. Then, too, the finding of retinal arteriosclerosis in patients with a normal or low blood pressure probably indicates, as in our sixteen cases, the existence of a previous hypertension with a subsequent myocardial weakening or loss of vascular tonus. This finding would have done much to solve the difficulty experienced by Janeway and others in deciding which arteriosclerotic patients had a low tension because of cardiac weakness and which had always had low tension. It is often of the greatest importance from the point of view of diagnosis, and particularly of prognosis, to be able to decide such a question. These facts also bring

out the great clinical difference that exists between arteriosclerosis confined to vessels of the first and second order of magnitude and those of the third.

Our results definitely establish the fact that the peripheral vessels play little or no part in hypertension. They do show, however, a definite relationship between small vessel sclerosis, indicated in the retinal arteries, and high blood pressure. Nothing was developed from these observations to prove whether hypertension comes first and sclerosis second, or vice versa. But they do get closer to the facts. Undoubtedly, many cases of essential hypertension which are said to be free from association with arteriosclerosis, in reality may have a considerable degree of sclerosis of the small blood vessels. Undoubtedly, too, there are many cases of early hypertension in which no sclerosis of the retinal vessels can be made out. We wish to call attention, however, to the findings of Cohen,⁴ who noticed the absence of any apparent retinal arteriosclerosis as observed through the ophthalmoscope but the presence of retinal arteriosclerosis in the same patient when the retina was observed microscopically. He also calls attention to the fact that choroidal arteriosclerosis was present without retinal arteriosclerosis, and when both were present the former was even more marked than the latter. One other thought arises in conjunction with this work. We must assume that this disorder of small vessels is more or less general. We cannot think for an instant that hypertension is associated only with sclerosis of the retinal arteries. These are probably, therefore, a fair index of small vessels throughout the body.

OBSERVATIONS ON PULSUS PARADOXUS (WITH SPECIAL REFERENCE TO PERICARDIAL EFFUSIONS)

I CLINICAL *

H W GAUCHAT, M D, AND L N KATZ, M D

CLEVELAND

The occasional occurrence of a marked respiratory variation in the amplitude of the pulse was first described in 1850,¹ and since that time many reports concerning its clinical significance have appeared. The opinions expressed in regard to the probable cause and significance of this phenomenon have been manifold, diverse, and often contradictory, so much so, perhaps, that modern writers seem inclined to look on the question of pulsus paradoxus as the remnant of an unfinished polemic. During the routine examination of a large number of patients coming into the hospital, we were impressed by the appearance of pulsus paradoxus in certain types of disease. Observations were therefore made on these patients, and animal experiments were devised to aid in the clinical interpretation of this interesting pulse phenomenon.

The first critical exposition of pulsus paradoxus was presented by Kussmaul² in 1874. His polygraphic records were not complete, but his detailed descriptions of three cases, including one previously reported by Griesinger,³ leave no doubt concerning the precise nature of the condition which he observed. Because of the prevailing misconception of Kussmaul's work and the vague manner in which many textbooks allude to the pulse which justly bears his name, it seems appropriate to quote from his original contribution. After thoroughly describing the pathologic entity of fibrous mediastinopericarditis with thoracic adhesions, he continues:

Clinically our affection of chronic inflammation of the pericardium and its obliteration, which is a criterion of mediastinitis, leads to a peculiar pulse phenomenon from time to time associated with unusual behavior of the neck veins. During the time that the sternum with each inspiration exerts a narrowing tug upon the ascending aorta or the arch, the pulse in all the arteries becomes regularly and rhythmically smaller, while the heart movements remain constant. Thus with each inspiration, at regularly repeated intervals, the pulse becomes smaller to return again with expiration. I propose, therefore, to call this the paradoxical pulse, partly because of the peculiar disproportion between the heart activity and the arterial pulse, partly because the pulse, in spite of the seeming irregularity, in reality has become a regularly recurring waxing and waning

* From the Medical Clinic of City Hospital, Western Reserve University

1 Williams, C J B London J Med 2 164, 1850

2 Kussmaul, A Berl klin Wchnschr 10 433, 445, 461, 1873

3 Griesinger, W, quoted by Kussmaul, Footnote 2

In the light of this excellent clinical and pathologic report, one is inclined to accept Kussmaul's use of the term "paradox" as legitimate in spite of the fact that it is frequently referred to as a "misnomer"⁴ or a "poorly chosen name"⁵. Such statements are not based on a fair appreciation of Kussmaul's work, and tend to discredit any clinical significance which this phenomenon may possess.

A great deal of discussion has appeared in the literature since this classical research. Clinicians and physiologists have endeavored to justify their own interpretations of the phenomenon, generally, however, with insufficient evidence to support them. Soon after Kussmaul's report, Sommerbrodt⁶ claimed that the so-called paradoxical phenomenon was in reality a normal event which could be found in nearly all healthy persons during deep breathing, especially those with powerfully developed thoracic muscles. Reigel⁷ observed it in a typhoid patient after severe hemorrhage, and believed that myocardial weakness played the important rôle in such cases. His main idea, however, was that the pulsus paradoxus was due to an incomplete filling of the aortic system which might result from a deep inspiration. Gaisböck's⁸ observations led him to conclude that this pulse is produced by a reflex vasomotor mechanism acting through the medullary center. He supposed that a peripheral constriction occurs during inspiration causing a diminished volume of the radial artery. Falconer and McQueen,⁹ Hewlett,¹⁰ P. W. Williams,¹¹ Edgecombe,¹² Harris,¹³ and others, reported observations on the decrease in volume in the radial arteries (usually in one only) during inspiratory movements of the thorax which have been shown to be the result of oval compression of the subclavian artery between the first rib and the clavicle. This feat is accomplished by practiced contortions of the thoracospacular groups of muscles and is necessarily limited to the arteries beyond the constricting point. Rosenbach¹⁴ proposed that kinking of the inferior vena cava by the contracting diaphragm would explain the inspiratory diminution in the arterial pulse wave in some cases. Traube¹⁵ and Wenckebach¹⁶ held that

4 Lewis, T. J. Physiol. **37** 233, 1908

5 Sahli, H. Treatise on Diagnostic Methods, Ed. 4, Philadelphia, W. B. Saunders Company, p. 126

6 Sommerbrodt, H. Berl. klin. Wchnschr. **14**: 615, 1877

7 Riegel, F. Deutsch. med. Wchnschr. **24** 345, 1903

8 Gaisböck, F. Deutsch. Arch. f. klin. Med. **110** 506, 1913

9 Falconer, A. W., and McQueen, T. M. Quart. J. Med. **8** 38, 1914

10 Hewlett, A. W. A Unilateral Paradoxical Pulse, J. A. M. A. **45** 1405 (Nov. 4) 1905

11 Williams, P. W. Brit. M. J. **2** 369, 1907

12 Edgecombe, W. Brit. M. J. **2** 890, 1920

13 Harris, T. Lancet **1** 1072, 1899

14 Rosenbach, O. Arch. f. path. Anat. u. Physiol. **105** 215, 1886

15 Traube, L. Berl. klin. Wchnschr. **13** 369, 1876

16 Wenckebach, K. F. Brit. M. J. **2** 369, 1907, Ztschr. f. klin. Med. **7** 402, 1910

adhesions, such as are found in mediastinopericarditis with obliteration of the sac, will directly embarrass the action of the heart by virtue of the tension which they exert on it during inspiration.

The apparent relationship between the pulsus paradoxus and intrapleural pressure variations has been pointed out by Wenckebach,¹⁶ Reichmann¹⁷ and others. Every one is familiar with the simple experiments of Valsalva and Muller, in which respiratory efforts are made with the glottis closed. However, the effects of these experiments on pulse volume and pressure have been variously interpreted. In fact, there has been a long period of controversy among physiologists concerning the exact effect of respiration on cardiodynamics.

After reviewing the literature, one feels that Kussmaul's original position remains valid, but there is sufficient evidence to suggest that as a diagnostic factor its possibilities should be more clearly defined and extended. One of the first logical steps in this direction was undertaken by Schreiber,¹⁸ who separated the "true" pulsus paradoxus from the "false" types. "True" pulsus paradoxus, he said, must conform to the following stipulations: (1) it must be felt in all accessible arteries, (2) it does not require a deep inspiration, (3) there must be no irregularity of the heart action. Thus he excluded the many case reports which involve compression effects on certain arteries, voluntary exaggeration of breathing, and pure sinus arrhythmias. Other observers¹⁹ have emphasized the important distinction between the dynamic type which results from respiratory conditions, modifying the intrapleural pressure, and the mechanical variety which is produced by the tugging of mediastinothoracic synechia on some part of the cardiac structures.

The appearance of a paradoxical pulse in patients with pericarditis, we have found to be of unusual significance. True, most of the controversy concerning pulsus paradoxus has centered around this pathologic condition, but curiously enough it appears that so much attention has been given to the adhesive forms that the serous types have been neglected. Our interest in the paradoxical phenomenon was first stimulated by the striking examples observed in patients with pericardial effusion.

DEFINITION AND CLASSIFICATION OF PULSUS PARADOXUS

In order to limit the discussion, we attempt to define and classify pulsus paradoxus. By a pulsus paradoxus, pulsus respiratio, or Kussmaul's pulse, we mean a rhythmical pulse which diminishes perceptibly in amplitude or is totally obliterated during inspiration in all palpable arteries. It is a periodic waxing and waning of pulse amplitude, which

¹⁷ Reichmann, E. Ztschr f klin Med **53** 112, 1904

¹⁸ Schreiber, J. Arch f Exper Path u Pharmak **12** 168, 1880

¹⁹ Wenckebach. Footnote 16 Semerau, M. Deutsch Arch f klin Med **115** 608, 1914

from the standpoint of clinical interest must occur without conscious effort on the part of the patient to modify his breathing. This diminution in pulse amplitude is always accompanied by a fall in systolic blood pressure. We wish to lay particular emphasis on the fact that we are dealing with a practical clinical problem, and therefore we exclude all pulse phenomena which cannot be detected by the palpating finger and likewise any instances in which the subject intentionally influences the character of his respiration.

CLINICAL CLASSIFICATION OF PULSUS PARADOXUS

The clinical material which we have gathered on this pulse phenomenon can be best arranged, we believe, as follows:²⁰

GROUP I Abnormal conditions of the respiratory system

- A Partial tracheal or bronchial stenosis bronchial spasms, laryngeal croup
- B Pathologic processes impairing lung extensibility pneumonia, chronic emphysema
- C Involuntarily exaggerated breathing
 - (1) Uncomplicated acidosis
 - (2) Associated with cardiovascular inefficiency severe hemorrhage, myocardial failure

GROUP II Pathologic conditions of the pericardium

- A Mediastinopericardial adhesions
- B Pericardial effusion
(Paramediastinal encapsulated pleural effusion)

PULSUS PARADOXUS ASSOCIATED WITH ABNORMAL CONDITIONS OF THE RESPIRATORY SYSTEM²¹

It did not seem advisable to report all our cases of pulsus paradoxus in statistical fashion, but rather to cite a few examples commonly seen in the clinic and to offer an interpretation of the phenomenon in these cases.

20 Congenital anomalies of the circulation, such as patent ductus arteriosus have been reported as a condition producing pulsus paradoxus. Francois-Franck (quoted by Reichmann, Gaz med de Paris, No 50, 1878), among others, believed that in such conditions the waxing and waning of the pulse was due to a shunting of aortic blood into the pulmonary artery during inspiration, thereby decreasing the volume of the aortic pulse wave. This explanation may be correct, provided a free flow of blood from the aorta occurs under such conditions. Cases of this nature are seldom observed, however, and a clinical diagnosis is difficult to establish. Furthermore, a recent experience has cast some doubt on the contention that pulsus paradoxus may be produced by a patent ductus arteriosus. Two cases of aneurysm of the sinuses of Valsalva which perforated into the pulmonary artery, causing a free anastomosis between the two vessels, have been intensively studied in this clinic. Neither of these showed a paradoxical pulse. Both came to necropsy and will be reported by Dr R W Scott.

21 Our animal experiments (Katz, L N, and Gauchat, H W Arch Int Med, this issue, p 371, have demonstrated conclusively that the intrapleural pressure is the prime factor responsible for the pulsus paradoxus in this group.

Partial Tracheal or Bronchial Stenosis (Group 1, A)—Pulsus paradoxus was frequently found in patients suffering from acute asthmatic attacks. The presence of a marked increase in the negative intrapleural pressure was evident in these patients by the retraction of the intercostal spaces, the narrowing of the costal angle and the vertebral movement of the sternum during inspiration. The prompt relief from this respiratory embarrassment which was secured by the administration of epinephrin resulted in a coincident disappearance of the paradoxical pulse.

Similar observations were made in cases of tracheal obstruction due to aneurysm of the transverse aorta or mediastinal tumor. We also observed a paradoxical pulse in children with diphtheria striving desperately to breathe against partial obstruction of the larynx. The dramatic relief given by intubation or tracheotomy was promptly followed by disappearance of the waxing and waning of the pulse. Gerhardt,²² in 1895, emphasized this manifestation of the pulse as an

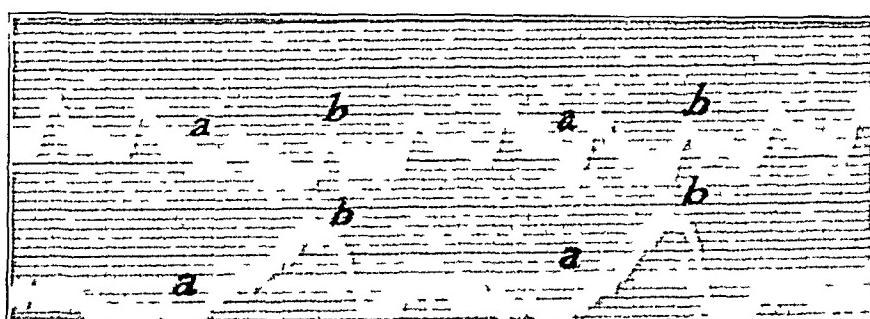


Fig 1.—Pulsus paradoxus in a patient with chronic bronchitis and emphysema. Upper curve is an optical record of the right radial artery obtained with Wiggers' pulse recorder (Wiggers, C J., and Baker, W R. Am J Physiol 59:454, 1922) and segment capsules. Lower curve of respiration was taken simultaneously by means of a cup tambour fastened over the epigastric region by an elastic band—upstroke inspiration, downstroke expiration. Vertical lines denote 0.1 of a second, horizontal lines 1 mm apart, *a*, beginning of inspiration, *b*, beginning of expiration.

indication of the onset of the stage of asphyxia in cases of laryngeal croup.

Pathologic Processes Impairing Lung Extensibility (Group 1, B)—We have found frequent instances of the paradoxical pulse associated with diseases which involve the parenchyma of the lung. A particularly striking example (Fig 1) was seen in a child with acute bronchopneumonia following measles. In this case, diffuse infiltration and consequent inextensibility of the bases of the lungs made it necessary for the patient to accomplish respiration entirely by the use of the thoracic

cage. The extraordinary effort required to ventilate a lung whose elasticity was distinctly reduced demanded an increase in the depth and the velocity of inspiration.

Pulsus paradoxus was found in all varieties of pneumonic infiltration. The fact that many cases of pneumonia do not exhibit the phenomenon suggests that the volume and elasticity of the unaffected lung areas may suffice to carry on respiration without causing an undue increase in the intrapleural pressure values. Although the respiratory rates which accompany pneumonic affections are usually rapid, this does not necessarily imply that the pleural pressure variations are appreciably increased. There is no practical clinical method of measuring intrapleural pressure, but careful attention to the patient's mechanism of breathing usually permits a reasonably accurate estimation.

While making observations in a large number of cases with well advanced pulmonary tuberculosis, we were somewhat surprised to find

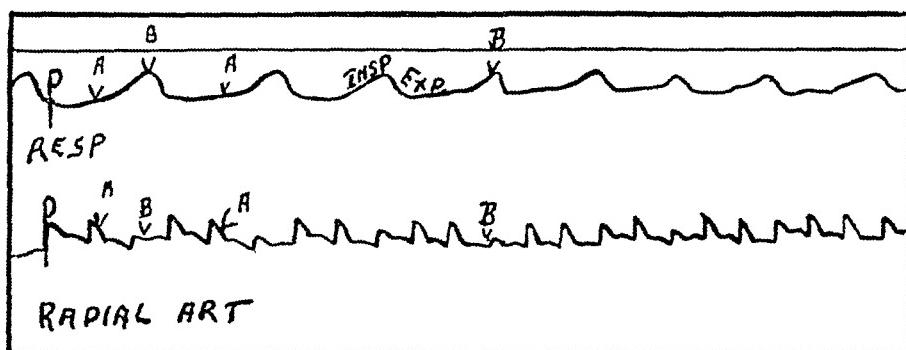


Fig. 2.—Pulsus paradoxus in a patient with diffuse bronchopneumonia. Record obtained as in Figure 1, except that a Mackenzie polygraph was used in place of the optical capsule. *P* denotes comparable points. Upper curve is respiration, upstroke inspiration.

that these patients did not have a paradoxical pulse. This may be due to the fact that the majority of tuberculous patients in spite of extensive parenchymal involvement do not, as a rule, have an increased *depth* of breathing. The slow process of infiltration and cicatrization probably allows ample time for the unaffected lung areas to assume the ventilatory function without an increase in intrapleural pressure variations.

Several patients with chronic emphysema were observed in periods of acute pulmonary decompensation at which time the pulsus paradoxus was quite marked (Fig. 2). On recovering from these attacks of severe bronchitis and the establishment of a fairly normal type of breathing, the paradoxical pulse disappeared entirely. It is not surprising that our cases of pulmonary emphysema exhibited the most marked examples of pulsus paradoxus seen under Group 1, when one

considers the nature of this pathologic condition. There is probably no chronic process which should be more effective in modifying intrapleural pressure values than chronic bronchitis and emphysema, for here we may have the combined effects of bronchiolar stenosis, rigidity of the lung, and an inefficient action of the diaphragm. In fact, the handicap offered to pulmonary expansion by these factors probably causes more marked changes in intrapleural pressure than might be suspected from examination of the patient.

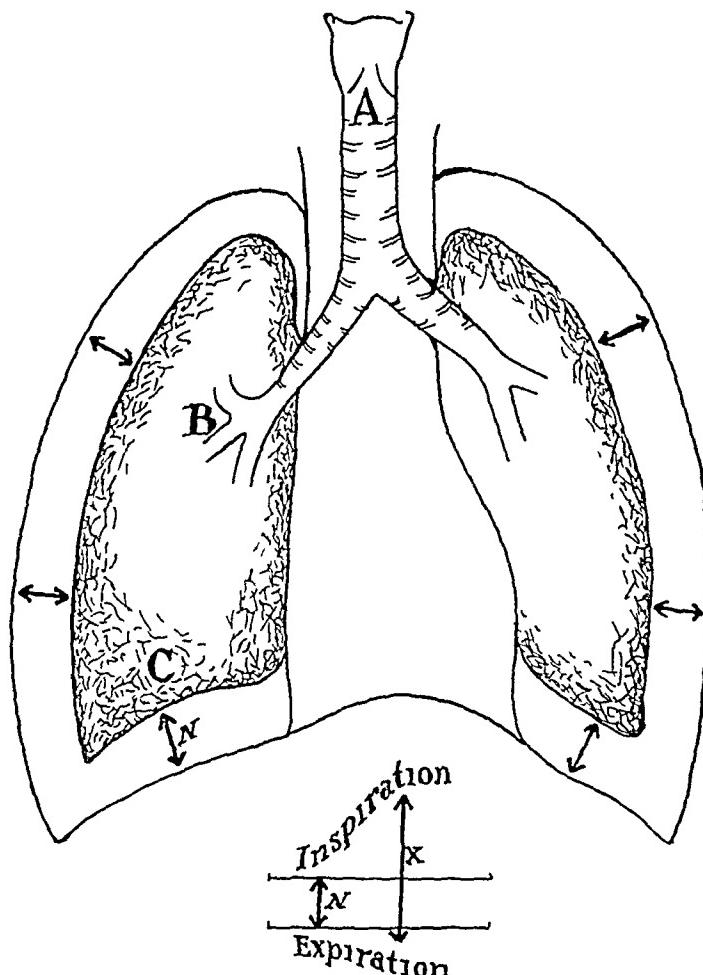


Fig 3.—Diagrammatic scheme of the respiratory mechanism. Arrows placed in the pleural spaces represent the variation in pressure during a normal respiration. N represents the normal variation, X , an exaggerated value which is sufficient to produce a pulsus paradoxus. The value X may be produced by increasing the excursion of the thorax by stenosis of the trachea or larynx indicated by A , by bronchial stenosis (B) or pulmonary infiltration (C).

Involuntarily Exaggerated Breathing (Group 1, C)—In the routine examination of patients suffering from renal or diabetic acidosis we frequently observed a pulsus paradoxus. We found some patients with renal acidosis, however, who had a considerable increase in the

tidal air, but because the *velocity* (that is the gradient of the variations in intrapleural pressure) was not increased (both inspiration and expiration being prolonged) there was no palpable variation in the pulse wave.

Respiratory and circulatory conditions occasionally combine their effects to produce a pulsus paradoxus. For example, we found a paradoxical pulse in patients under anesthesia, who had lost much blood. It was also commonly present in cases of surgical shock. Moribund patients in the stage of cardiovascular collapse frequently exhibited a pulsus paradoxus.

Comment.—We have indicated in the foregoing presentation that certain well known types of respiratory disease are frequently associated with a pulsus paradoxus. The one factor common to all these conditions is an abnormal variation in intrapleural pressure. The cause of this increase may be due to stenosis of the air passages or involvement of the pulmonary parenchyma, as pointed out in the foregoing discussion and diagrammatically represented by A, B and C in Figure 3. We have denoted the normal intrapleural pressure variation in this figure by "N," and we may assume on the basis of animal experiments given in another report that whenever this is increased to the hypothetical value "X," we may expect a pulsus paradoxus to result, regardless of the exact physical defect in the respiratory mechanism. In certain cases, marked circulatory inefficiency may play the leading rôle in the production of a paradoxical pulse.

The precise manner in which the variations in intrapleural pressure manifest themselves in the peripheral pulse, we shall leave for discussion in the report of our animal experiments. For practical purposes, it is sufficient to know that the presence of an increased intrapleural pressure variation may adequately explain the clinical production of pulsus paradoxus.²³

It follows, therefore, that in order to offer a correct interpretation of the paradoxical pulse phenomenon as it occurs in respiratory diseases, certain signs must be looked for. Is respiration thoracic or abdominal? Do accessory muscles participate in the respiratory act? Is there retraction of the intercostal spaces? What are the evidences of excursion and activation of the diaphragm? Is the velocity of inspiration and expiration increased? Obviously, it is only by such a careful analysis of the mechanism of breathing that one can make a reasonable clinical estimate of the intrapleural pressure variation at the bedside.

23 The phenomena of cardiorespiratory interference waves recently reported by Gesell and his associates may, as they suggest, be explained on a similar basis (Trotter, R. T., Edson, P., and Gesell, R. Am J Physiol 60: 500, 1922).

PULSUS PARADOXUS ASSOCIATED WITH PATHOLOGIC CONDITIONS OF THE PERICARDIUM

We wish to present several detailed case reports of pericarditis. These were selected from our series because they include the various clinical forms, and moreover because they illustrate clearly the relation of pulsus paradoxus to pericardial pathology.

MEDIASTINOPERICARDIAL ADHESIONS (GROUP II, A)

CASE 1—History—J. S., white, a carpenter, aged 28, admitted to the hospital on Aug 28, 1922, with a diagnosis of chronic fibrous mediastinopericarditis, became ill six months prior to admission, with shortness of breath, pain in the chest, cough, and an attack of hemoptysis which sent him to a hospital. His condition remained about the same, and after two weeks he returned home, where he had been gradually declining up to the time of his admission.

Physical Examination—The patient was a well developed, undernourished man, propped up in bed in a comfortable attitude. An irritating cough, pain beneath the lower end of the sternum, and shortness of breath on exertion were his chief complaints. There was some edema of the dependent parts and the face. Respiration was increased in rate (26 per minute) and was predominantly thoracic in type, with impaired undulatory movement of the upper right ribs. In spite of these variations from the normal, the patient's breathing efforts were quiet and regular. The pulse was small and monocratic in type, with a palpable waxing and waning during tranquil breathing. Blood pressure was systolic, 120, diastolic, 80. The jugular bulb was not distended and exhibited a normal pulsation. A feeble apical impulse was perceptible in the anterior axillary line in the fifth intercostal space, and a systolic impulse and diastolic impact were felt over the area of the second and third left intercostal spaces bordering on the sternum. The percussion boundary of the heart extended to the left anterior axillary line in the fifth interspace. The right boundary of cardiac dulness formed an obtuse angle with hepatic dulness at a level with the fourth rib 4 cm from the sternum. Auscultation of the cardiac area revealed distinct sounds at the base and apex. Reduplication of the second sound, which was only occasionally present over the base of the heart, was the only variation from normal. The liver margin was 3 cm below the right costal border, firm and not tender. The spleen was not enlarged.

Roentgen-Ray Examination—A large, ill-defined, pyramidal heart shadow was found encroaching on the lung areas at the bases. No pulsation was seen under the screen. Both costophrenic sinuses were cloudy. Excursion of the diaphragm was limited. Surrounding lung areas were "hazy" in character, except the right apex, which had a moderately dense cloudiness. The most unusual feature of the plate was the "shaggy" and indistinct margin of the cardiac area, which fused with the pulmonary shadows, making it difficult to determine its exact outline.

Subsequent Course—The diagnosis of chronic mediastinopericarditis was made, with the suspicion that there might be some effusion into the sac. However, this was early excluded by ineffectual attempts to remove fluid by tapping at these points. To the right of the sternum in the fourth interspace, the trochar lodged in the auricle, and venous blood was obtained. In the left fifth interspace, the needle "grated" against the ventricular musculature. A puncture was made by inserting the trochar underneath the tip of the xiphoid cartilage through the subcardial diaphragm. By this means, 2 ounces (60 c.c.) of serosanguineous fluid were aspirated, presumably from the pericardial sac.

Sept 11, 1922. The patient's general condition improved after a course of digitalis therapy. He was up in wheel chair. Pulsus paradoxus was observed in the erect and prone positions.

September 19 There were signs of fluid at the right lung base and 800 c.c. of clear serous effusion were removed, the specific gravity of which was 1.016. Pulsus paradoxus was still present.

September 29 Thoracentesis of the right pleural cavity (1,200 c.c.) was performed. The pulse was unchanged.

October 19 The patient's general condition was worse. There was fluid in both pleural cavities and the abdominal cavity. Abdominal paracentesis (2,500 c.c. of bloody serous exudate) was performed.

October 26 There was great difficulty in swallowing. Cyanotic, generalized edema and dyspnea were present.

On October 29 the patient died.

Synopsis of Postmortem Examination.—The heart and pericardium were universally adherent and firmly attached to the sternum, weighing together 630 gm. The pericardium was greatly thickened, particularly over the region of the coronary sulcus, at which place it was 10 mm thick. At the apex and over the auricles the average thickness was 4 mm. The posterior portions of the pericardial membrane consisted of a layer of caseous material, and caseous tubercles were found on the anterior surface of the heart. Both lungs were everywhere adherent to the chest wall and mediastinal structures. Costophrenic sinuses and the subcardial diaphragm were covered with thick fibrous and caseous exudate. There were found also miliary tuberculosis of the spleen, peritoneum, liver and omentum, chronic vegetative mitral valvulitis, tuberculous ulceration of the cecum, chronic passive congestion of the viscera and general anasarca.

Comment.—This clinical picture as well as the postmortem findings bears a striking resemblance to Kussmaul's² cases. We were unable to find any particular relation of the mediastinal adhesions to the arch of the aorta such as Kussmaul described, and thus could not confirm his contention that the pulsus paradoxus results from a kinking of the aorta by the cicatricial bands encircling it.

In another case in this group an inspiratory distention of the neck veins was observed, a phenomenon which Kussmaul also pointed out, and which he properly attributed to the mediastinal synechia.

PERICARDIAL EFFUSION (Group II, B)

CASE 2—History.—J. S., colored, a mill worker, aged 23, was admitted to the hospital on July 31, 1920, with a diagnosis of chronic tuberculous pericarditis with effusion and tuberculous peritonitis and pleurisy with effusion. The patient had been ill for the past three months with cough, pain over the right hypochondrium, and increasing shortness of breath, all of which began with a "cold" contracted while working at a hot furnace. He had always been well until the onset of this illness.

Physical Examination.—The patient was sitting comfortably in bed, with no particular signs of illness. His breathing was slightly increased in rate (24 a minute), quiet and regular, and predominantly thoracic. The pulse showed a palpable waxing and waning with respiration in all accessible arteries. Blood pressure during expiration was systolic, 118, diastolic, 85. The pulse rate was 90. The neck veins were somewhat distended but with normal pulsations. The tension within the jugular bulb decreased during inspiration. The temperature was 38.4°C. (101.2°F.), but the patient did not feel feverish. Chest examination revealed a large flat area of cardiac dulness extending as far as the midaxillary line on the left, and 3 cm to the right of the sternum, where it merged with the dulness of a pleural effusion which extended up to the level of the third intercostal space anteriorly and the fifth rib in the postaxillary line. The precordial

area was flat to percussion, as much as at Louis' angle as over the lower segment of the sternum. No visible or palpable cardiac impulses were present. The heart sounds were faintly audible, and no murmurs were heard. The left lung base posteriorly had a tympanitic percussion note. The inferior border of the liver was 2 cm above the umbilicus, with its edge rotated downward, so that it could be palpated only with difficulty.

Roentgen-Ray Examination.—An immense pyriform cardiac shadow, which did not pulsate, was observed under the fluoroscopic screen. A fluid shadow was present in the right pleural cavity, and there was a faint cloudiness over both lung areas.

Subsequent Course.—The patient remained in the hospital for one year prior to his death. He began to decline about a month after admission, on account of a dissemination of the tuberculous infection, which gradually invaded the lungs, pleura and peritoneum. The serous cavities were tapped on numerous occasions to relieve the embarrassed respiration. Six weeks before he died, a total of 7,000 cc of serosanguineous fluid were withdrawn in one day, 5,550 cc from the abdominal cavity, 1,000 cc from the left pleural cavity and 450 cc from the pericardial sac. A guinea-pig inoculated with the pericardial fluid died of tuberculosis.

This case was repeatedly used for the demonstration of pulsus paradoxus to junior medical students, and the disappearance or abatement of this phenomenon after tapping was demonstrated by the house physicians, who performed pericardial paracentesis on six occasions. Twelve hundred cubic centimeters was the largest amount removed from the precordial sac at any one time. During the last few months, the patient suffered from circulatory stasis and dyspnea. The pulse became small and rapid, so that the paradoxical effect was not a prominent feature. He died on June 25, 1921.

Synopsis of Postmortem Examination.—The pericardial sac was considerably enlarged, greatly thickened (6 mm), and contained about a pint of clear serous fluid. The posterior portion of the sac was adherent to the heart, and the epicardium over the anterior surface was covered by a layer of caseous material 2 mm thick. All of the mediastinal structures, especially the great vessels, were so densely adherent that it was necessary to remove them en masse.

The heart was small (not weighed), and had the characteristic appearance of brown atrophy. The endocardium, heart valves and aorta were uninvolved. There was found also serofibrinous pleuritis with bilateral sacculated effusions, discrete pulmonary tuberculosis—both apices, atelectasis of the lower lobe of the left lung, caseous tuberculosis of the thoracic and abdominal lymph nodes, serofibrinous peritonitis with ascites (4 liters), chronic passive congestion of the viscera, perilobular cirrhosis of the liver and general anasarca.

CASE 3—History.—M. Z., a white man, a laborer, aged 60, was admitted to the hospital on Nov 20, 1919, with a diagnosis of tuberculous pericarditis with effusion. The patient said that his trouble began three weeks before admission with cough, fever and chills, and pain over the lower portion of the sternum. The irritating, unproductive cough did not allow him to sleep, and during the past few days aphonia and dysphagia developed. Previously he had always been well and he was accustomed to hard work.

Physical Examination.—The patient, a well nourished man, about 60 years of age, was reclining comfortably in bed. His respiration was 26, pulse rate, 96, temperature, 37°C (98.6°F). His cheeks, lips and ear lobes had a peculiar dusky hue, which has been aptly described as a peach-skin complexion. There was slight supramalleolar edema. The rapid, small volume pulse manifested a striking waxing and waning, being almost entirely obliterated during his tranquil inspiratory efforts. The jugular bulb became distended when the patient assumed the recumbent position. Examination of the thorax revealed a pyriform area of precordial dulness, moderate emphysema of the lungs, and moisture at both

lung bases On auscultation over the central region of the sternum a soft to and fro friction rub was heard The liver was displaced downward, which caused a prominence of the epigastrium

Roentgen-Ray Examination—This examination substantiated the clinical impression of a large pericardial effusion encroaching on both lung areas A faint cloudiness in the right apex was suggestive of a thickened pleura

Subsequent Course—Because of the rather abrupt onset and the patient's good condition, it was thought at first that he suffered from an acute infection of the pericardium The subsequent course, however, disproved the tentative diagnosis On the third day after his admission, paracentesis of the pericardium was performed, and 500 c.c. of clear, serous effusion were withdrawn the specific gravity of which was 1.015 Fluid was still flowing from the needle, but it was thought advisable not to remove more at this time Observations were made on the pulse, respiration and vital capacity, and it was found that these were not materially altered by the paracentesis, except for a decided lessening of the respiratory variation in the size of the pulse

This excellent demonstration of the effect of a pericardial effusion on the pulse was repeated no less than thirteen times during a period of several months, amounts varying from 200 c.c. to 1,000 c.c. being withdrawn on each occasion The paradoxical nature of the pulse never completely disappeared, but whenever the aspiration amounted to 500 c.c. or more, the many house physicians and students who usually witnessed the procedure noted a decided lessening in the waxing and waning of the pulse The patient experienced considerable subjective respiratory relief, and frequently insisted that he should be tapped Curiously enough, his heart always maintained a consistently rapid rate (from 94 to 116) regardless of the fluid content of the pericardial sac His general condition permitted him to walk about the hospital during the day, and he enjoyed a tolerably good physical condition for one year

During the last four months of his illness, the patient showed a rapid decline due to tuberculous invasion of the peritoneum and colon The pericardial condition remained about the same up to the time of his death, March 8, 1921

Synopsis of Postmortem Examination—The pericardial sac was dilated, thickened and fibrosed It contained 500 c.c. of bloody serous exudate, but was apparently capable of holding about a liter when filled The heart was fairly free in the sac, and the epicardium contained small tubercles and adherent fibrinous tags There was little caseation about the mediastinum, the extensive pericardial and pleural process being mostly fibrinous in character The heart, with its thin layer of fibrinous exudate, weighed 325 gm All chambers were dilated, and the myocardium was the seat of fatty degeneration The endocardium was uninvolved, except for sclerotic thickening of the aorta and mitral valve leaflets There was moderate senile sclerosis of the aorta There was found also serofibrinous peritonitis, tuberculous ulceration of the intestines and colon, acute peritonitis due to perforated ulcer of the ileum and chronic passive congestion of all viscera

Comment—We were privileged to observe these two similar cases throughout the entire period of illness Frequent tapping of the pericardium demonstrated the intimate relationship existing between a distended pericardial sac and pulsus paradoxus Necropsy examinations furnished conclusive evidence of the exact nature of the pathologic processes The amount of fluid in these cases was found to be considerably less than the quantity actually removed from the sac during the earlier part of the patients' illness The recognition of this fact suggests that many case reports of pulsus paradoxus attributed to the synechia found

at necropsy are open to criticism because the quantity of fluid present during the course of the disease cannot be correctly judged from the necropsy examination alone.

CASE 4—History—E. B., a colored man, a laborer, aged 28, was admitted to the hospital on Dec 7, 1921, with a diagnosis of chronic tuberculous pericarditis with effusion and chronic tuberculous pleurisy with effusion. The patient walked into the hospital complaining of slight shortness of breath on exertion, a sensation of heaviness in the epigastrium, night sweats and general malaise. He attributed his condition to a "bad cold" beginning one month previously with "pleurisy pains" and a cough which still persisted. The patient had always been well and accustomed to hard work.

Physical Examination—The patient, a tall, stalwart negro, sat comfortably on the edge of his bed. The first thing that impressed those who examined him was the remarkable waxing and waning of the pulse, whereas his breathing would have passed as natural except for a slight increase in rate. The jugular veins were distended and pulsating slightly. Chest examina-

TABLE 1—*Observations Made During Withdrawal of Pericardial Fluid (Case 4)*

Time	Quantity Withdrawn in Cc	Mc in Pericardial Pressure in Millimeters of Serous Effusion (Specific Gravity 1.025)	Remarks
10 05 a.m.	Anastomosis with manometer made	90 mm	Pulsus paradoxus palpable in all arteries*
10 10	100	80 mm	Patient perspiring*
10 15	30	70 mm	No effect on pulse*
10 20	(Total 130 c.c.)	75 mm	Pulsus paradoxus still palpable
10 25	70	45 mm	Pulsus paradoxus decreased
10 40	(Total 200 c.c.)	30 mm	Pulsus paradoxus cannot be palpated*
10 55	110	10 mm	Venous pulsation noticed in jugulars
11 10	(Total 310 c.c.)	0	General condition good*
	150		
	(Total 400 c.c.)		
	275		
	(Total 735 c.c.)		
	50		
	(Total 785 c.c.)		

Patient returned to ward, and rested better than usual during the night.
* Optical records were made at these points.

tion revealed an extensive area of cardiac dulness, with absence of pulsation, and faintly audible heart sounds. The right side of the chest was flat to percussion below the fifth rib in the midaxillary line. The liver was rotated downward.

Roentgen-Ray Examination—This examination corroborated the presence of pericardial and pleural effusions.

Paracentesis of the Pericardium—An ordinary long lumbar puncture needle, containing a tight fitting stilette, was inserted into the pericardium at a point 3 cm to the left of the sternum in the fifth interspace. A single calibrated glass tube of 4 mm bore was used as a manometer. A glass T-tube was interposed in the rubber tubing connecting the hilt of the needle to the manometer, and from this point the fluid was aspirated with a 200 cc glass syringe. Pinch cocks were used to keep the systems alternately closed off during aspiration and reading of the manometer. The heart motion could be felt against the shaft of the needle, and the point was presumably in the lowest portion of the pericardial sac near the diaphragm.

Table 1 gives the results of the operation described above, and in Table 2 we have noted the important physical factors which were observed during this procedure. The tables were made at the time of the operation, and the data

are self-explanatory. The disappearance of the paradoxical pulse on removing the fluid is of particular significance. The optical records taken at the designated intervals confirmed the impression of three observers who attended to palpation of the pulse. The paradoxical character of the pulse reappeared the next day, but not to the degree previously noted.

The patient stayed in the hospital a few weeks longer, and his general condition improved slightly. He was readmitted on Feb 2, 1922, because of shortness of breath on exertion and a "heavy feeling in the right chest." A pulsus paradoxus was present. Thoracentesis of a large pleural effusion gave considerable subjective relief, but had no influence on the pulse. Table 3 gives the data on this procedure. A few days later his pericardium was tapped in two places

TABLE 2—*Observations Before and After Paracentesis of the Pericardial Sac (Case 4)*

Observation	Before Paracentesis	Immediately After Removal of 785 Cc
Pericardial pressure	94-99 mm	0 mm
Pulse rate	110	114
Pulse amplitude	Moderately small	Increased
Arterial pressure	140-100 mm	132-98 mm
Lateral boundaries of cardiac dulness	Left midaxillary line	2 cm outside midclavicular line
Lower margin of liver	4 cm below right costal margin	Edge felt at level of right costal margin
Respiratory rate	34	32
Type of breathing	Predominantly thoracic 1,740 c.c.	Thoracic abdominal 1,825 c.c.
Vital capacity	Distended with slight visible pulsation	Pulsating with decreased distention
Neck veins	Fairly good	Breathing feels much easier with disappearance of the "heavy" sensation in epigastrium
General condition		

TABLE 3—*Effect of Thoracentesis of Right Pleural Cavity on Pulsus Paradoxus (Case 4), 1,654 Cc Clear Serous Effusion Withdrawn (Sp. G. 1016)**

Observation	Before Thoracentesis	After Withdrawal of Fluid
Fluid pressure	110-107 mm	5-2 mm
Fluoroscopy	Density in lower half of right lung	Lung practically clear, large pear-shaped cardiac shadow
Pulse rate	114	112
Respiratory rate	36	34
Blood pressure	145-110 mm	145-110 mm
Vital capacity (sitting)	1,700 c.c.	1,850 c.c.
Pulsus paradoxus	Readily palpable	Unchanged

* Patient sitting up in bed in a comfortable position, needle inserted at right tenth intercostal space in midaxillary line, fluid slowly aspirated into a 100 cc syringe following the thoracentesis; breathing felt easier to the patient, and there was evidence of excursion of the right diaphragm.

and no fluid obtained except venous blood from the auricle.²⁴ During the remainder of his stay in the hospital, his right pleural cavity was tapped four times, and an average of 1,100 cc of serous effusion removed each time, but without effect on the pulsus paradoxus. He requested his discharge on March 10, 1922.

CASE 5—*History*—G. H., a colored man, a laborer, aged 31, was admitted to the hospital on Aug 22, 1922, with a diagnosis of chronic tuberculous peri-

24 We were somewhat at a loss to explain our inability to obtain fluid from the pericardium at this time in spite of the indications of its presence by physical signs and roentgen-ray findings. Perhaps the two months that had intervened since the last successful paracentesis allowed the heart to become adherent anteriorly, thus obstructing access to a posterior collection of fluid.

carditis with massive pericardial effusion. This patient had had influenza in 1917, with prompt recovery. In 1920, he had had a chancre which he had treated himself. He considered his general health very good until two months before admission, when he began having pain in the abdomen, dizziness, night sweats and shortness of breath on exertion. He kept at his work until the day preceding his admission, when a severe spell of breathlessness forced him to give up.

Physical Examination.—The patient was a large, muscular type of negro, sitting in bed, in no apparent discomfort. His temperature was 37.4°C (99.3°F). Pulsus paradoxus was striking regardless of whether the patient was in a prone or erect position. When attempts were made by this patient to adapt his respiration as nearly as possible to the thoracic or abdominal type, the paradoxical character of the pulse remained unmodified. The jugular bulb was moderately distended and refilled from the cardiac end when obliterated by stroking with the finger.

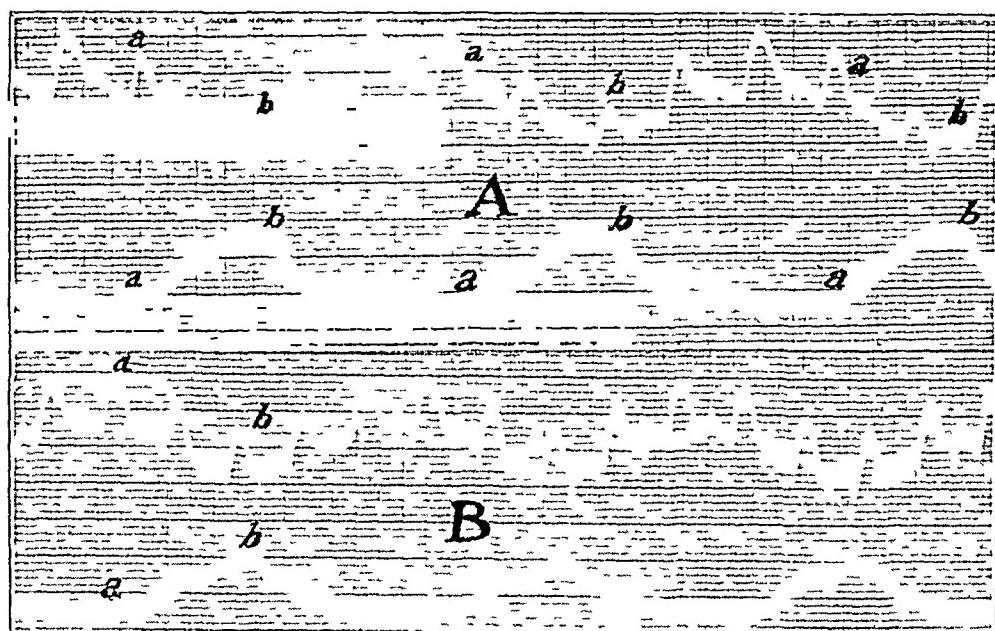


Fig 4.—Optical record of pulse and respiration immediately before and after removal of 950 cc of fluid from the pericardial sac (Case 5). Record obtained as in Figure 1. Vertical lines 0.2 of a second apart. A shows pulsus paradoxus before removal of fluid and B its complete disappearance following paracentesis of the pericardium. Shifting base line of the pulse curve is an artefact caused by movements of the wrist.

Percussion of the thorax revealed a large flat cardiac area extending to the midaxillary line on the left, and on the right to the midclavicular line, forming an obtuse angle with the liver dulness. The excursion of the upper four ribs was accentuated but symmetrical on the two sides, and there was inspiratory narrowing of the costal angle. The percussion note of the left lung base was impaired posteriorly, with fine crepitant râles on auscultation of this area. The lower margin of the liver was percussed but not palpated 2 cm above the umbilicus.

Röntgen-Ray Examination.—An immense pyriform cardiac shadow which did not pulsate was observed under the screen. The small lung areas shown in the plate were fairly clear. The findings were quite characteristic of a large pericardial effusion.

Paracentesis of the Pericardium—On Aug 28, 1922, the pericardium was tapped according to the technic described in Case 4. The observations made during this procedure are shown in Table 4. The disappearance of the pulsus paradoxus was the most striking feature observed, as shown in the optical tracings of the pulse (Fig. 4).

The pericardial sac promptly refilled, and the patient was tapped again on several occasions. The observations noted at the first tapping were confirmed each time. The patient left the hospital four weeks after admission at his own request.

Comment—The therapeutic experiments in these two cases demonstrate clearly that the pericardial effusion was the direct cause of the paradoxical phenomenon, since pulse rate, blood pressure, respiration and all other factors of importance remained practically unchanged, while the paradoxical character of the pulse disappeared. The observations made on thoracentesis in Case 4 indicated that the presence of a large free pleural effusion had no effect on this pulse phenomenon.

TABLE 4.—Effect of Paracentesis of Pericardial Sac on Pulsus Paradoxus (Case 5), 950 C c Serosanguineous Fluid Removed (Sp Gr 1.022)

Observation	Before Paracentesis	Immediately After Paracentesis
Pulsus paradoxus	Marked*	Absent*
Pericardial pressure	78-74 mm	74 mm
Pulse rate	100	110
Pulse volume	Moderate	Increased
Arterial pressure	Expiration 130-88 mm, Inspiration 110-88 mm	Not recorded
Fluoroscopy	Immense pear shaped heart shadow	Much diminished in size
Lower liver margin	4 fingers below right costal margin	2 fingers higher
Respiratory rate	24	24
Vital capacity	1,450 c c	Not recorded
Neck veins	Inspiratory distention	Less distention, slight pulsation
General condition	Fairly good	Breathing easier

* See Figure 4 for optical records of respiration and pulse.

Analysis of the pulse tracings in these cases shows that they all have the same time relationship to respiration. The change in pulse amplitude always takes place in the first or second beat after the onset of the respiratory phase²⁵.

CASE 6—*History*—N. E., a white man, a clerk, aged 36, was admitted to the hospital on Oct 27, 1922, with a diagnosis of acute septicemia and acute purulent pericarditis. About three weeks before admission, an abscess had formed on the axillary surface of the right arm. The patient became quite sick with fever and chills, and the abscess was incised. The local condition improved, but his general condition became rapidly worse.

25 This applies to all cases of pulsus paradoxus (both Groups I and II) which we have studied. We mention it here to dispel any ideas concerning a possible temporal difference in the paradoxical pulse curves found under different clinical conditions. However, we have noted a variability in the degree of change in pulse amplitude. As a rule, the cases in Group II showed a more striking fluctuation in the size of the pulse than those in Group I.

Physical Examination—The patient was a well developed man presenting the picture of a severe acute infection and who was at times irrational. The incised abscess was entirely healed. The temperature was 40.2°C (104.3°F). His respiration was 30. The pulse rate was 134. The leukocyte count was 16,000. Blood culture showed *Staphylococcus aureus*. The impression was that the patient was suffering from an acute septicemia, which probably originated from the abscess in the right arm.

Subsequent Course—Nov 4, 1922. The patient developed a pulsus paradoxus, and an audible friction rub was heard over the fourth rib to the left of the sternum. Swallowing became so painful that fluids were given by hypodermoclysis. There was cardiac dulness 2 cm to the left of the midclavicular line and at the right margin of the sternum.

November 7. Pericardiocentesis was performed in the left fourth intercostal space 2 cm from the sternum. Fifty cubic centimeters of turbid straw colored fluid containing pus cells and numerous gram-positive cocci were withdrawn. *Staphylococcus aureus* was obtained from culture of the pericardial fluid.

November 9. There was marked pulsus paradoxus. Two hundred and fifty cubic centimeters of purulent fluid were withdrawn from the pericardial sac, without any effect on the pulse. The condition of the patient made it inadvisable to remove more fluid. The blood pressure was systolic, 118, diastolic, 80 before and after removal of fluid. Signs of infiltration were developing at the base of the left lung.

November 12. The patient died.

Synopsis of Postmortem Examination—The pericardial sac was distended and contained 850 cc of seropurulent fluid. No adhesions were present. The parietal pericardium was of normal thickness, and the epicardium was covered by a thin layer of fibrinopurulent exudate. There was found also acute seropurulent pleuritis, left, 500 cc, multiple abscesses of lungs, focal, purulent nephritis and myocarditis, acute splenic hyperplasia and duodenal ulcer.

Comment—This case illustrates the diagnostic importance of pulsus paradoxus associated with acute infectious conditions. Without the proper interpretation of the patient's pulse, the early discovery of the purulent effusion probably would not have been made. Paracentesis was of little benefit here, because of the multiple foci of infection throughout the body. However, similar cases have been reported cured by surgical drainage of the pericardial sac, and it is interesting to note that such a case was presented before the Royal Medical and Chirurgical Society in 1883.²⁶ In this case particular emphasis was placed on the fact that free drainage of 2 liters of pus from the pericardium at once relieved the urgent symptoms, and the pulsus paradoxus, which had been striking, immediately disappeared.

PARA MEDIASTINAL PLEURAL EFFUSION

CASE 7—History—R. B., a colored man, a laborer, aged 36, was admitted to the hospital on Sept 12, 1921, with a diagnosis of universal mediastino-pericarditis with obliteration of sac (necropsy), chronic fibrous pleuritis with encapsulated left pleural effusion and pulmonary tuberculosis. The patient was sent to the hospital for active pulmonary tuberculosis. During the past few months he had noticed increasing shortness of breath and edema of the legs. He suffered in addition from constant severe pain across the lower portion of the sternum.

Physical Examination—The patient was a medium sized, undernourished colored man in an orthopneic position. His temperature was 38.2°C (100.7°F). Breathing was accomplished almost entirely with the upper portion of the thoracic cage. There was a vertebral retraction of the sternum. Examination of the lungs revealed the lower margins of the bases to be higher than normal, with a total absence of tidal excursion. There was evidence of an active tuberculous infiltration at the right apex.

The cardiac area of dulness extended 1 cm beyond the anterior axillary line on the left and 2 cm beyond the right margin of the sternum, where it formed a right angle with hepatic dulness. The apical impulse was not palpable, but the impulse and impact over the base of the heart was rather pronounced. The heart sounds were distant at the apex without friction rubs or murmurs. The pulse was rapid (110), of small volume, monosystolic in type, and exhibited a decided respiratory waxing and waning. The jugular bulb was notably distended, with slight pulsation. The enlarged liver made a definite epigastric prominence and was tender to palpation. There was dependent edema of the extremities and back.

Roentgen-Ray Examination—A large rounded cardiac shadow was noted, which almost filled the entire left side of the chest and extended slightly beyond the right margin of the sternum. It formed approximately a right angle with the right diaphragm. The costophrenic sinuses were clouded and indefinite in outline. There was some cloudiness of the right apical region suggestive of tuberculosis.

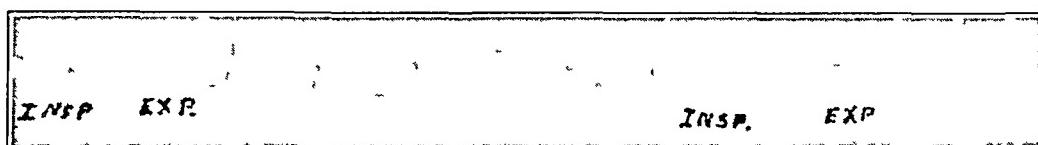


Fig 5.—Pulsus paradoxus in a case of encapsulated paramediastinal effusion (Case 7) Pulse recorded as in Figure 1

Course of Illness—The diagnosis of pericardial effusion was made on the basis of the large area of cardiac dulness and the pulsus paradoxus. The rather unusual left-sided situation of the effusion was attributed to dense pleural adhesions. As the patient's cardiorespiratory symptoms were becoming more urgent, paracentesis was indicated. Accordingly, he was tapped in the left fourth intercostal space 5 cm from the margin of the sternum, and 650 cc of serous exudate were removed. The paradoxical character of the pulse was markedly diminished by this procedure, and the subjective symptoms temporarily improved.

During the eight weeks that the patient was in the hospital, it was necessary to tap him every four or five days to give relief from steadily progressing symptoms of circulatory embarrassment. An average of 600 cc of serous fluid were withdrawn each time. Two days prior to his death, which occurred on Nov 16, 1921, he was tapped again to relieve the urgent symptoms of cyanosis, air hunger, edema "brust beklemmung," etc., which Kussmaul² described as the terminal condition in his patients. The result of this procedure is given in Table 5. Figure 5 is an optical record of the pulse taken before paracentesis. Unfortunately curves were not obtained to show the pulse change afterward.

Synopsis of Postmortem Examination—On opening the thorax, a large firmly encapsulated effusion was found in the left pleural cavity in close contact with the entire left side of the heart. The pleura was everywhere markedly thickened, especially along the mediastinum, the walls of the sac being 3 mm in thick-

ness. The diaphragmatic pleura was completely adherent and 5 mm thick. The right lung was completely adherent to the diaphragm and parietal pleura. Discrete tuberculosis was found at the apex of the right lung. The heart was entirely covered by the smooth, hard and greatly thickened pericardium. The pericardial sac was completely obliterated. The heart and pericardium together weighed 675 gm. The cut surface of the pericardium was composed of several layers of different character, the middle layer being yellow and structureless and the outer layers gray, fibrous and edematous. The pericardium varied from 1 cm to 2 cm in total thickness, being thinnest over the auricles and great vessels and thickest over the right ventricle. The myocardium was soft and brown, the wall of the left ventricle measuring 11 mm. The chambers of the heart were reduced in size. Microscopic examination confirmed the diagnosis of tuberculous pericarditis. There was found also extensive caseous enlargement of the mediastinal lymph nodes, discrete fibrous tuberculosis of the left apex, passive congestion and edema of the lungs, chronic passive congestion of all the viscera, and nutmeg liver.

TABLE 5.—*Effect of Paracentesis of Paramediastinal Pleural Sac on Pulsus Paradoxus (Case 7), 810 C c Serosanguineous Fluid Withdrawn (Sp G 1 025)*

Observation	Before Paracentesis	After Paracentesis
Pulsus paradoxus	Marked*	Slightly palpable
Fluid pressure (in mm of pleural exudate)	120-113 mm	0-24 mm
Pulse rate	110	120
Pulse volume	Very small	Increased
Arterial pressure	110-100 mm	110-90 mm
Right border of cardiac dullness	2 cm to right of sternum	At right margin of
Left border	1 cm beyond anterior axillary line in third interspace	2 cm within anterior axillary line sternum
Respiratory rate	32	32
Type of respiration	Mainly thoracic	Thoraco abdominal
Vital capacity	1,500 c c	Not obtained
Lower margin of liver	Edge palpable at umbilicus	2 cm higher
Neck veins	No pulsation marked engorgement	Pulsation with less distention
General condition	Cyanosis, dyspnea, edema, very restless	Not improved

* Figure 5 shows pulse record from radial artery.

Comment.—Necropsy examination of this patient revealed a pathologic condition which was not suspected from clinical observations. What we interpreted in the physical examination as a pericardial effusion was, in reality, an encapsulated pleural effusion. From the anatomic point of view, this is an extra-pericardial process, but in this case it had by virtue of its unique relation to the heart the same physiologic effect as a pericardial effusion, as indicated by the marked improvement in the pulse following paracentesis.

It is important, however, to consider the influence of the obliterative pericarditis which was also present in this case. Although removal of the fluid did not cause complete disappearance of the pulsus paradoxus, it had a pronounced effect in modifying the phenomenon. Consequently, we may state that of the factors concerned, the evidence strongly indicated that the primary rôle was played by the paramediastinal effusion.

GENERAL COMMENT

The foregoing cases illustrate the intimate relationship existing between pericarditis and the pulsus paradoxus. Our studies of these patients confirm the generally accepted opinion that cicatricial mediastinopericarditis is responsible for the paradoxical pulse in certain cases. An analysis of the hospital necropsy reports wherein adhesive pericarditis was present with no previous clinical evidence of a pulsus paradoxus strongly suggested to us that the absence of this physical sign in such cases was due to lack of adhesions to mobile portions of the thorax.

The observations made on paracentesis of the pericardial sac demonstrated quite conclusively that the effusion in these patients was directly responsible for the production of pulsus paradoxus. It is well known, however, that cases of pericarditis with effusion may not be associated with this pulse irregularity, and we have observed such patients. These exceptions can be accounted for by the fact that the quantity of fluid in these cases is not sufficient to raise the *pressure* within the sac to an effective level. Thus, under the conditions of a diseased and dilated sac, a surprising amount of fluid may be present without producing a pulse variation. The critical factor, we believe, is the degree of increased intrapericardial tension, which in turn is dependent on the thickness and distensibility of the parietal pericardium. The exact manner in which the pulsus paradoxus is produced under such circumstances will be analyzed more completely in the report of our animal experiments.

The striking clinical contrast which these cases afford when compared with those of Group I has been repeatedly emphasized in our case reports. In few cases of pericarditis did we find the evidence of a marked increase in pleural pressure variations such as was exhibited in the pathologic respiratory conditions. To find a person with no apparent respiratory discomfort exhibiting a definite respiratory waxing and waning of the pulse is in our experience strongly indicative of pericardial effusion.

SUMMARY AND CONCLUSIONS

1 Opportunity was afforded during the routine examination of a considerable number of patients to observe many instances of a respiratory variation in pulse amplitude. The frequency with which it was encountered in certain clinical conditions stimulated an attempt to evaluate its diagnostic importance.

2 In this report we have offered a definition of pulsus paradoxus which restricts the phenomenon to a simple respiratory waxing and waning of the pulse found under ordinary clinical circumstances. Cases

exhibiting the pulsus paradoxus are classified under two groups, the one associated with abnormal conditions of the respiratory system, and the other with pathologic affections of the pericardium

3 The suggestion is made, chiefly on the basis of experimental work given in the following paper, however, that the pulsus paradoxus associated with abnormal conditions of the respiratory tract is primarily caused by modifications of the intrapleural pressure variation. A clinical estimate of abnormal variations in intrapleural pressure may be obtained by analysis of the mechanism of breathing.

4 Pulsus paradoxus was found in cases of mediastinopericarditis with thoracic adhesions.

5 Clinical studies proved conclusively that effusion into the pericardial sac is directly responsible for a striking manifestation of the paradoxical pulse as evidenced by the disappearance of the pulse phenomenon after tapping the sac. The essential factor required to produce this phenomenon appears to be the increase in intrapericardial tension.

6 The unusual feature of pulsus paradoxus associated with pericardial effusion is its singular occurrence in patients presenting no clinical evidence of respiratory discomfort.

7 We therefore conclude that a pulsus paradoxus unaccompanied by exaggerated respiratory efforts may be regarded as a diagnostic sign of pericardial effusion.

OBSERVATIONS ON PULSUS PARADOXUS (WITH SPECIAL REFERENCE TO PERICARDIAL EFFUSIONS)

II EXPERIMENTAL *

L N KATZ, M D, AND H W GAUCHAT, M D

CLEVELAND

In the preceding report¹ which deals with pulsus paradoxus as observed in the clinic, it was pointed out that this pulse is of some diagnostic value, provided it is properly interpreted. Pulsus paradoxus was defined as a rhythmic pulse occurring in natural breathing which shows a waxing and waning in size during respiration, evident on palpation in all the accessible arteries. A classification of pulsus paradoxus was given, and emphasis was laid on its occurrence in large pericardial effusions. In the course of the foregoing study, several questions arose which could not be satisfactorily answered by the clinical data. For instance, we were unable to determine which circulatory changes are responsible for the pulse phenomenon, and we were certain neither of the factors involved nor of how such alterations in circulation take place.

Experimental studies of pulsus paradoxus are conspicuously few. In a careful review of the literature, only three such attempts were found. In 1878, Riegel and Tuczek² obtained a waxing and waning of the pulse by experimentally obstructing the trachea. Rosenbach,³ in 1886, observed a variation in pulse size when he injected large quantities of oil into the pleural sac, and also when he inflated a balloon previously inserted into the pleural cavity. Hoke,⁴ in 1912, repeated the experiments of Riegel and Tuczek and obtained similar results. Moreover, he noted a decrease in the pulse when he applied traction on the pericardium and also when he compressed the superior vena cava. His deductions are open to criticism, because the evidence which he presented is incomplete.

In the present report we give the observations and conclusions obtained on reproducing this pulse phenomenon experimentally in nineteen dogs. A pulsus paradoxus was produced in various ways but always with the view of reduplicating the clinical conditions as much as practicable.

* From the Physiological Laboratory, Western Reserve University, School of Medicine

1 Gauchat, H W, and Katz, L N Arch Int Med, this issue, p 350

2 Riegel, F, and Tuczek, F Berl klin Wchnschr **15** 739 and 771, 1878

3 Rosenbach, O Arch f path Anat u Physiol **105** 215, 1886

4 Hoke, E Wien klin Wchnschr **25** 998, 1912

I EXPERIMENTAL OBSERVATIONS PERTAINING TO THE PULSUS PARADOXUS IN CHRONIC ADHESIVE MEDIASTINOPERICARDITIS

Clinicopathologic studies have shown clearly that dense adhesions extending between the heart and the thoracic parietes are frequently associated with pulsus paradoxus.¹ There has been some controversy, however, as to whether or not this pulse phenomenon occurs only when the adhesions are attached directly to the large blood vessels. In fact, it is not quite clear whether or not kinking of the various vessels is equally effective. The effect of adhesions as found in clinical cases was simulated experimentally by applying traction to the pericardium and by compressing the various vessels arising from the heart, namely, the ascending aorta, pulmonary artery, pulmonary veins and the venae cavae. The effect of these manipulations on the carotid pulse was observed, particular attention being given to the time interval elapsing before the change in the pulse was apparent.

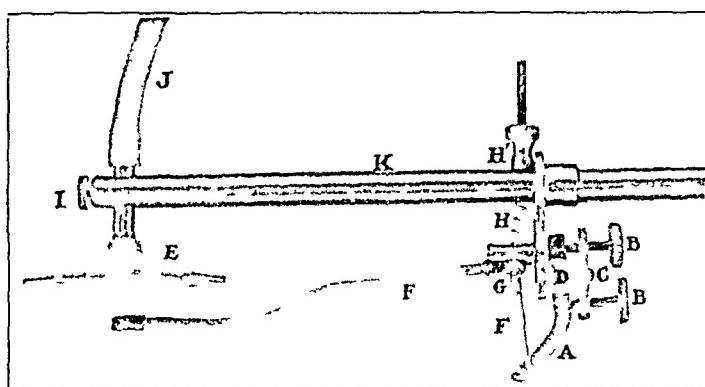


Fig 1.—Pulse recorder (one-third of actual size). The carotid artery dissected free and *in situ* is placed in the groove of the lower end of the rod (A), which is adjustable by means of two set screws (B) placed in bar (C) on either side of fulcrum (D). The lateral excursion of the artery is transmitted to the cup tambour (E) by means of an L-shaped aluminum bar (F) swinging on a knife edge fulcrum (G). The tension of the lever is adjusted by means of screw and spring (H, H'). The cup tambour can be lowered or raised, its position being fixed by set screw (I) which is fastened into the supporting bar (K). (J) is the tubing which transmits the pressure changes in the tambour to an optical segment capsule.

Method.—For this purpose, the animals were anesthetized with morphin and chlorethane, and artificial respiration was instituted, and the entire thoracic cage opened. The various tractions and compressions were manually performed during the apnea which followed slight over-ventilation of the animal.

Most of the records were obtained optically, although the earlier ones were taken on a smoked drum. The moment of manipulation was at first marked on the drum by one of us as signaled by the other. In

order to make the results more accurate, an electric signal was used later. The pulse was registered in several ways. The smoked drum tracings were recorded by connecting a Hurthle manometer with the carotid artery. The optical records were obtained with segment capsules either through the agency of a pulse recorder (Fig 1) constructed on the same principle as the model devised by Wiggers and Baker⁵ for clinical records of the radial pulse or with the aid of an arterial plethysmograph similar to the one described by Van Zwaluwenberg and Agnew⁶.

Results.—Obviously, manipulation of the aorta resulting in its partial occlusion is always followed by an immediate change in the carotid pulse. The alteration in pulse size which follows compression (or release of compression) of the pulmonary veins is not apparent at once but in the first or second beat after the manipulation. As a rule, it was found that if the manipulation occurs during systole of the ventricle or

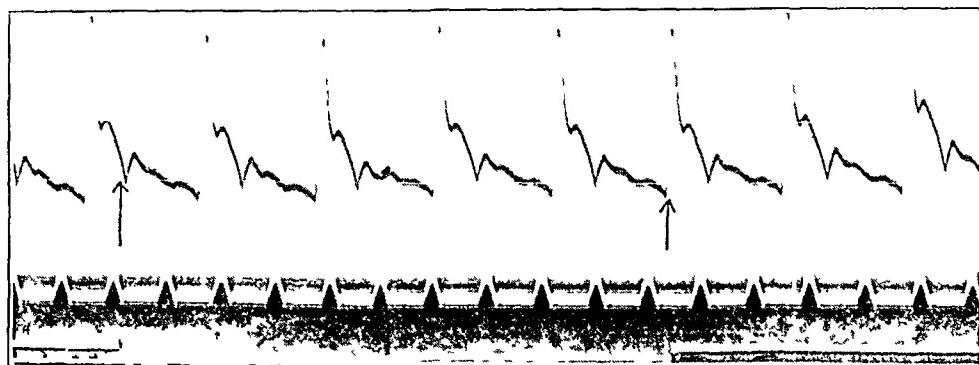


Fig 2 (Exper 311-16).—Record of carotid pulse showing the effect of manipulating the right pulmonary veins. Downward movement of base line in this and the following figures indicates the moment of compression, and the upward movement the moment of decompression. These points are also indicated by arrows. Pulse recorded by plethysmographic method. Time in tenths of a second.

during early diastole, the effect is apparent in the next beat, as shown in Figure 2. However, if the manipulation occurs late in diastole, the change is not noticed until the second beat, as illustrated in Figure 3. The effect of pinching the pulmonary artery is also apparent in the systemic pulse after the first or second beat. Manipulation of either of the venae cavae does not produce such an abrupt response, the pulse change not appearing until the third (as in Fig 4) or fourth beat following the compression.

Interpretation.—The time intervals between manipulation of the various vessels and the effect on the carotid pulse are summarized diagrammatically in Figure 5. The decrease in the pulse following com-

5 Wiggers, C. J., and Baker, W. R. Am J Physiol **59** 454, 1922.

6 Van Zwaluwenberg, J. C., and Agnew, J. H. Heart **3** 343, 1912.

pression of the pulmonary veins is obviously due to the fact that this compression immediately diminishes the supply of blood to the left side of the heart and indirectly the next ventricular discharge. This response to compression of the pulmonary veins is delayed until the second beat, when the manipulation occurs in the last part of the ventricular diastole because the ventricle at this time is already filled to

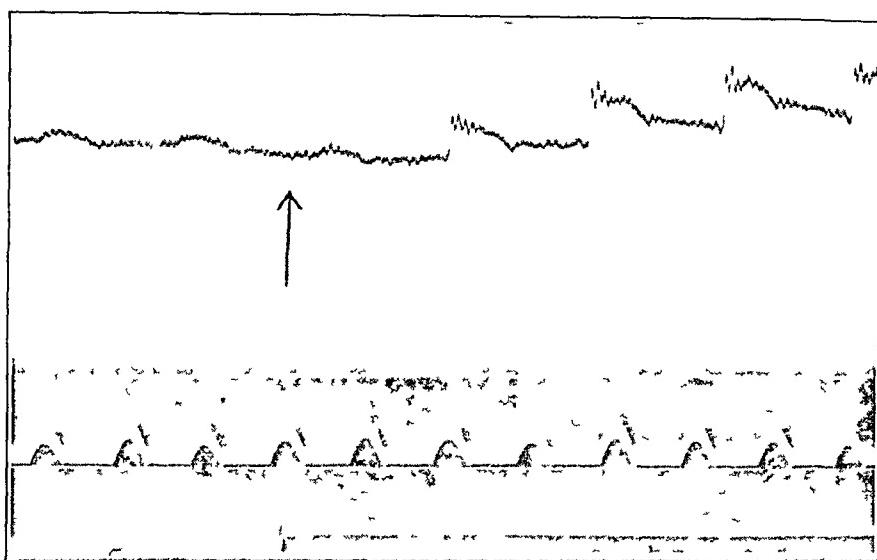


Fig 3 (Exper 311-9) —Record of carotid pulse showing the effect of decompression of the pulmonary veins. Pulse obtained by means of the pulse recorder shown in Figure 1

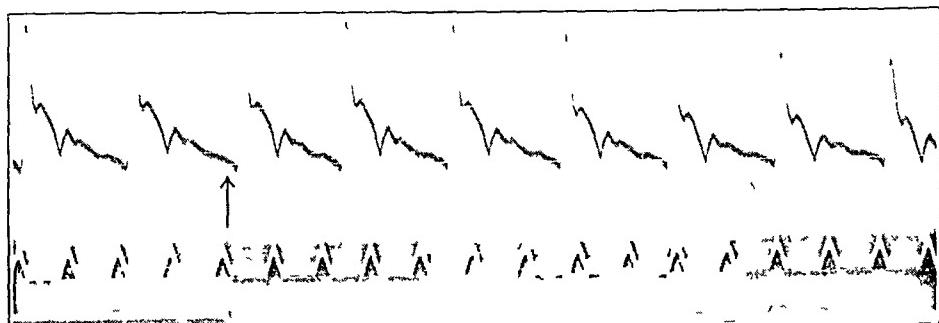


Fig 4 (Exper 311-15) —Record of carotid pulse, obtained as in Figure 2, showing the effect of compressing the inferior vena cava

capacity. The longer delay which follows compression of the venae cavae is due to the added time interval required for the altered blood flow to pass through the pulmonary circuit and reach the left side of the heart.

Traction on the Pericardium—It was found that when sufficient traction is used on the pericardium, a change in the pulse size occurs in the first or second beat after the traction is applied. The time at

which the change appears in the pulse suggests that the effect is produced by kinking either the pulmonary vessels, the aorta or both—and not by partial obstruction of the venae cavae

It is noteworthy that this time interval is the same as that found in clinical cases of pulsus paradoxus associated with mediastinopericardial adhesions. We are therefore justified in concluding that in such patients inspiration causes a kinking in the pulmonary vessels, the aorta or both

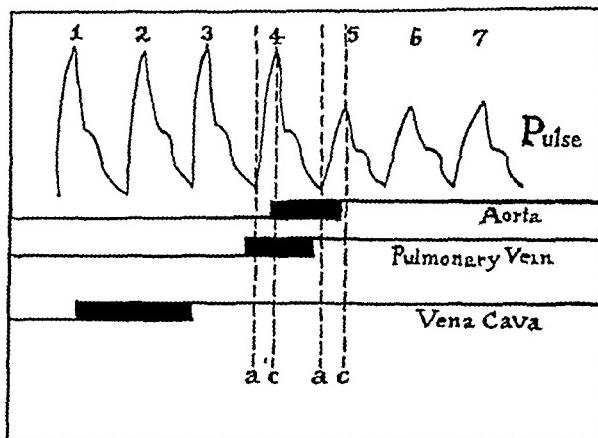


Fig 5.—Diagram showing the time relation between compression of the various blood vessels and the appearance of the effect in the pulse (*a*), marks the beginning of the anacrotus, (*c*), the beginning of the catacrotus. Blocks indicate time limits within which compression must occur in the respective vessels in order to produce a decrease in the size of the fifth pulse beat

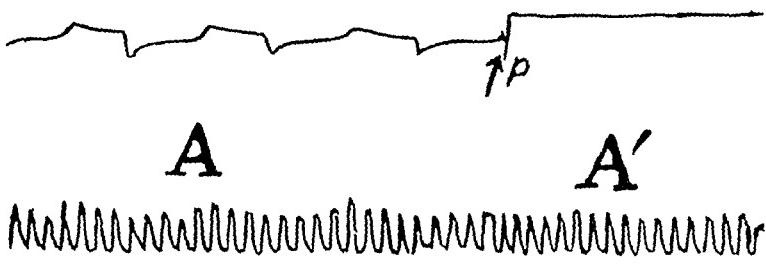


Fig 6 (Exper 304 0, 0')—Tracing showing the effect of manipulating the diaphragm on the carotid pulse during apnea, when the thorax was closed (*A*) and after bilateral pleural fistulae were made (*A'*). The time at which the fistulae were made is indicated by the arrow. The upper curve indicates the intrapleural pressure, downstroke, inspiration, lower curve, carotid pulse recorded with Hurthle manometer, *p*, corresponding points. Time in tenths of a second. In *A*, intrapleural pressure varied from -40 mm of saline to -10 mm, in *A'* the intrapleural pressure was 0 mm

We do not infer by this that an inspiratory obstruction of the venae cavae does not occur, but that the effect of this on the pulse is probably always overshadowed by the more immediate effect of the inspiratory kinking of the other vessels. Whether the change in pulse size in some

cases is due to kinking of the aorta and in others to partial occlusion of the pulmonary vessels, or whether these two causes share equally in all cases, cannot be decided by studying the pulse. Our observations do show, however, that the adhesions need not be attached to any particular vessel but may be fastened anywhere between the cardiac structures and the thoracic parietes and still be capable of producing a pulsus paradoxus.

II EXPERIMENTAL OBSERVATIONS PERTAINING TO THE PULSUS PARADOXUS IN EXAGGERATED BREATHING

Clinical investigation has shown conclusively that exaggeration of the depth of breathing is a common cause of pulsus paradoxus,¹ and the pulse phenomenon in this condition has been commonly attributed to an increased variation of intrapleural pressure (Baumler,⁷ Reichmann,⁸ Semerau,⁹ Wenckebach¹⁰). However, a few writers have taken exception to this. Gaisböck,¹¹ for instance, thought it was a nervous phenomenon, and Rosenbach³ believed that it was due to a kinking of the inferior vena cava by the inspiratory contraction of the diaphragm. In the present report, the various factors in respiration which are known to exert an influence on the circulation were therefore considered individually in order to ascertain which of them is primarily responsible for the pulsus paradoxus.

After determining what we believe to be the chief respiratory factor, the next problem was to decide the manner in which it acts on the circulation. In the past, the paradoxical pulse has been ascribed to alterations in the capacity and resistance of the intrapulmonary vessels (Höke⁴), to modifications of the venous flow into the chest (Schreiber¹²), to changes in the capacity of the aorta and intrathoracic arteries (Reichmann⁸), and to variations in the venous return to the left side of the heart (Baumler⁷). An accurate study of the time factor, that is, the relation of pulse changes to the respiratory cycle, will eliminate most of these. In the preceding section, it was pointed out that the time interval between manipulation of the large blood vessels and the effect on the pulse is different in the various vessels concerned, but characteristic for each. The place in the circulation at which the changes primarily responsible for the paradoxical pulse occur can therefore be determined by noting with which of these time relationships the pulse phenomenon coincides.

7 Baumler, C. *Deutsch Arch f klin Med* **14** 455, 1874

8 Reichmann, E. *Ztschr f klin Med* **53** 112, 1904

9 Semerau, M. *Deutsch Arch f klin Med* **115** 608, 1914

10 Wenckebach, K. F. *Ztschr f klin Med* **71** 402, 1910

11 Gaisböck, F. *Deutsch Arch f klin Med* **110** 506, 1913

12 Schreiber, J. *Arch f exper Path u Pharmacol* **12** 168, 1880

Method—Natural respiration and the closed chest was used in most instances. The depth of respiration was increased by asphyxiating the animal, by producing a partial pneumothorax or, in most cases, by partial tracheal obstruction. The hyperpneic stage of Cheyne-Stokes respiration, which fortunately developed spontaneously in several animals, was also available. The pulse was recorded as before. Records of respiration were obtained, except in a few cases, by means of a pleural cannula, which was connected by a T-tube both to a tambour writing on a smoked drum (or to a segment capsule in the optical tracings) and to a U-tube saline manometer. Direct readings of the latter were obtained before the tracing was inscribed, in this way giving the actual values of the intrapleural pressure. The tube leading to the manometer was closed when a record was taken in order to avoid distortion of the respiratory curve.

Relation of Changes in Size of Pulse to Depth of Respiration—As a rule, no pulse inequality was apparent under control conditions. In some dogs, however, slight variations in pulse size occurred even with natural unexaggerated breathing, particularly in those animals which were severely traumatized or had been under deep anesthesia for some time. In all cases increasing the depth of breathing augmented these variations or induced a waxing and waning in the pulse when none had been present before (Figs 7 A and B and 8). In general, the amount of variation in pulse size was proportional to the depth of breathing, provided other conditions remained unchanged. As a rule, the more deficient the circulation the less the extent of intrapleural pressure variation necessary to produce a pulsus paradoxus, confirming our clinical observations¹³.

The Respiratory Factor Responsible for the Changes in Pulse Amplitude—1. Intra-Abdominal Pressure. Elimination of intra-abdominal pressure variations by opening the abdomen was not sufficient to prevent the occurrence of a pulsus paradoxus. For example, in the first half of Figure 7 C, the paradoxical pulse was produced by the hyperpnea resulting from partial pneumothorax. The fact that the abdomen had been previously widely opened in this animal did not prevent the appearance of the pulse phenomenon.

The unimportance of intra-abdominal pressure was further demonstrated by comparing the effect of abdominal and thoracic breathing on the pulse. Abdominal breathing was favored by restricting manually the expansion of the chest, and thoracic breathing by restricting the

13 In addition to the change in pulse amplitude, the pressure records show a fluctuation of the diastolic pressure (base line), the extent of which parallels the degree of variation in pulse size. Wiggers' tracings obtained from the pulmonary artery show somewhat similar changes (Wiggers, C. J. Am. J. Physiol. 30: 233, 1912).

abdominal movements In these experiments, it was found that neither type of breathing produced any changes in pulse size except when the depth of breathing was increased, and in the latter case, the pulse change occurred regardless of which type of respiration was increased

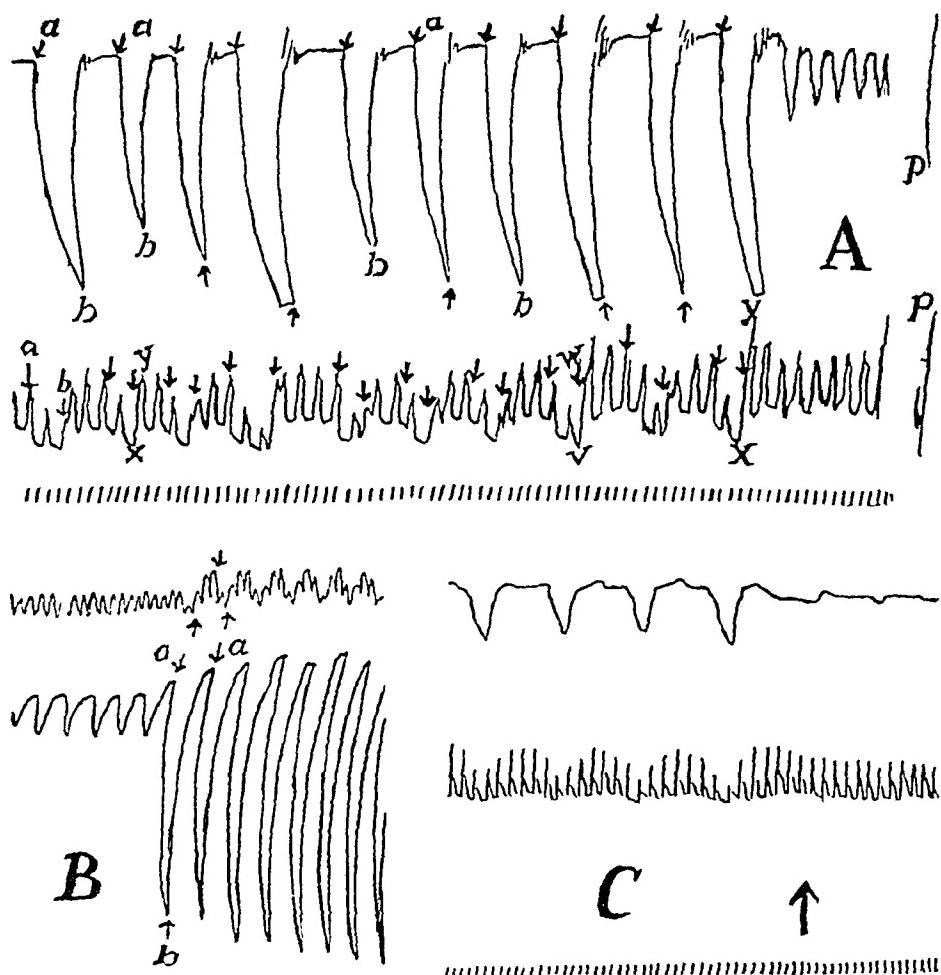


Fig 7.—Segment A, Exper 304 G. The first portion of tracing shows the effect of tracheal obstruction on the carotid pulse, the last portion is a control after release of obstruction. The upper tracing indicates intrapleural pressure, upstroke, inspiration, downstroke, expiration. The lower curve indicates the carotid pulse recorded as in Figure 6. Time in tenths of a second. P, comparable points, a, beginning of inspiration, b, beginning of expiration, other lettering explained in text.

Segment B, Exper 302 F and G. The last portion of the tracing shows the effect of tracheal obstruction on the carotid pulse, the first portion is a control, upper curve, carotid pulse, lower curve, intrapleural pressure. Lettering as in segment A.

Segment C, Exper 304 P, P'. The first portion of the tracing shows the effect of an induced partial pneumothorax on the carotid pulse in an animal with an open abdomen and closed thorax whose pericardium contained 90 cc of oil under 30 mm of positive pressure. Intrapleural pressure varied from -80 mm saline to -40 mm at the time that the first portion of the curve was obtained. The second portion was taken after bilateral pleural fistulae were made, intrapleural pressure, 0 mm. The arrow indicates the point at which the holes were cut in diaphragm. Upper and lower curves as in segment A.

2 Diaphragm Our findings in regard to the diaphragm are shown by the following typical experiments. Experiment 304 0, 0' (Fig. 6) was performed on an animal with the thorax intact but with opened abdomen. During a period of apnea which followed slight overventilation, the central tendon of the diaphragm was grasped on its under surface and its position rhythmically changed, simulating in this way its normal respiratory excursion. A slight variation in pulse size resulted as shown by the pulse curve in tracing (A), but it was associated with a slight variation in intrapleural pressure (upper tracing). The excursion of the diaphragm, however, failed to produce any variation in pulse size (A') after the pleural pressure variations were eliminated by bilateral pleural fistulae.

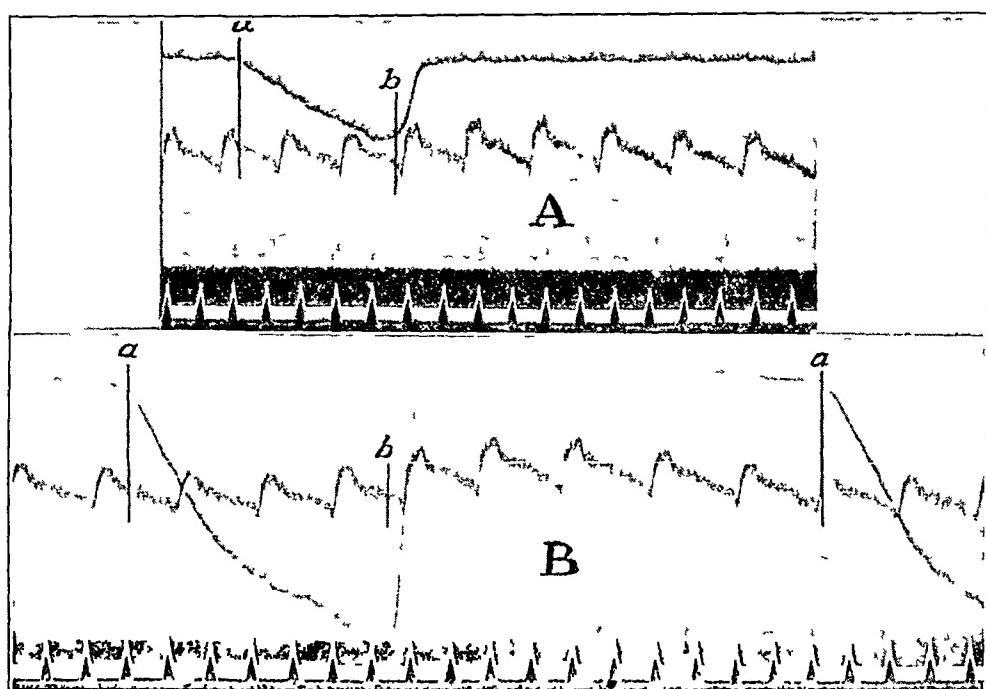


Fig. 8 (Exper. 309-4, 7)—Optical record showing the effect of partial tracheal obstruction on the carotid pulse. A indicates control, B, partial tracheal obstruction; upper curve, intrapleural pressure, downstroke, inspiration; lower curve, carotid pulse obtained with pulse recorder shown in Figure 1. Time is shown in tenths of a second. Lettering as in preceding figure. In A, the intrapleural pressure varied from -16 to -56 mm of saline and in B from -10 to -160 mm.

Experiment 303, A, was performed on an animal in whose thorax windows 4 inches (10 cm) in diameter were made in order to eliminate intrapleural pressure variations as well as changes in lung volume. Violent movements of the diaphragm occurred in this animal as a result of asphyxia, and yet no change in pulse amplitude appeared in the tracing.

Experiments, of which these are typical examples, indicate that, contrary to the opinion of Rosenbach,³ the diaphragm is not the essential factor responsible for the pulsus paradoxus.

3 Lung Volume The effects of changes in lung volume on the circulation which have been extensively studied by Cloetta leave no doubt that the resistance and capacity of the intrapulmonic vessels vary during respiration (Wigger¹³) The present investigation is concerned with the effect of these changes on the peripheral pulse

Moderate artificial respiration was found to produce a variation in pulse amplitude in animals when the chest was closed, but none when the thorax was open. For example, in experiment 307, B and C, mild artificial respiration produced some variation in the size of the pulse when the thorax was closed. This was eliminated when the ribs were resected. In Experiment 303, B and C, the pulse was uniform in size when mild artificial respiration was instituted in the presence of open, bilateral pleural fistulae, but when the fistulae were closed a respiratory variation in pulse size appeared. Experiments such as these demonstrate that a moderate variation in lung volume per se does not affect the systemic pulse¹⁴.

4 Intrapleural Pressure Thus, by a process of elimination, we are left with intrapleural pressure as the respiratory factor which produces the pulse phenomenon. A consideration of the foregoing presentation shows that elimination of the respiratory variation in intrapleural pressure was always followed by the disappearance of any previously existing variation in pulse amplitude. Another example of this is shown in Figure 7 C. A pulsus paradoxus was produced in a naturally breathing animal by inducing a partially closed pneumothorax (first part of Fig 7 C). At the point indicated by the arrow, two large holes were made in the diaphragm. This procedure eliminated the intrapleural pressure fluctuations (upper tracing) and at the same time the inequality of the pulse (lower curve), and yet, while the record was taken, the animal breathed as before.

We therefore conclude that the respiratory factor primarily responsible for the pulsus paradoxus in exaggerated breathing is the fluctuation of intrapleural pressure.

Time Relation of the Change in Pulse Size to the Respiratory Phases—The changes in the pulse are illustrated in Figure 7 A, which was obtained in a dog during marked tracheal obstruction. The results in this experiment are typical of those found throughout, although more marked than usual. This figure, as well as Figures 7 B and 8, shows that the changes in diastolic pressure (base line of pulse

13 Wiggers, C J Physiol Rev 1 239, 1921

14 Large variations in lung volume, as is generally recognized, produce changes in the size of the pulse in open chested animals. For example, in Experiment 307, F, in which the lung volume during inflation was about twice that during deflation, a noticeable variation in pulse size was observed. Such extreme changes in lung volume probably never occur clinically or in animals with closed chests.

curve) coincide with the onset of changes in intrapleural pressure and are in the same direction and roughly proportional. This exact coincidence of the changes of diastolic pressure with the phases of respiration indicates that these changes are due to an effect on the aorta and intra-thoracic arteries, in that manipulation of the ascending aorta gave a like relationship (note Fig. 5). The sudden increase in intrapleural pressure during expiration causes a rapid expulsion of blood from the chest and therefore a coincident sharp rise of diastolic pressure. When the effect of expiration is synchronous with the upstroke of the pulse, a larger pulse wave results, for example, $x-y$ in Figure 7 A. This larger pulse has often been erroneously interpreted as an increased systolic discharge of the heart, the respiratory factor being overlooked. A similar effect on the pulse can be readily produced by coughing, and such records were obtained by us on several occasions.

With regard to pulse size with which we are primarily concerned, the change does not coincide with the beginning of the phase of respiration but occurs either in the first or second beat after its onset. Thus, when the beginning of expiration comes early in diastole, as in Figure 8, and in the third, fifth, sixth and seventh expiration in Figure 7 A, the next beat is larger. When the onset of expiration comes late in the diastole or at the onset of the systole, as in the first, fourth and ninth expirations in Figure 7 A, the increase in pulse beat is not apparent until the second beat. Finally, when expiration begins with ventricular ejection, the resulting beat is larger, owing to a summation of ventricular ejection and the effect of the sudden expiration on the aortic capacity, as pointed out above. Analysis of the curves presented will show a like time relationship at the beginning of inspiration. Expiration was selected in the foregoing discussion only because it brings out the changes in a striking manner.

The Significance of the Temporal Relationship.—The time relation found in exaggerated breathing coincides with that found on manipulating the pulmonary veins (as will be seen on comparing the observations outlined above with the diagram, Fig. 5), indicating that the variation in pulse amplitude in this condition is due directly to a modification of the venous return to the left ventricle.

Further confirmation of this interpretation is given by the fact that a similar relationship between pulse and respiration was found in this series, regardless of the number of beats per respiratory cycle. In fact, a similar relationship was found in our clinical cases, in which an even wider range of respiratory and pulse rates was obtained. Furthermore, in clinical cases (and animal experiments) in which Cheyne-Stokes respiration appeared, the first inspiration coming after an apneic period was associated with a decrease in pulse size, which began in the beat following the inspiration.

The last observation excludes the possibility of the pulsus paradoxus being due to a delayed effect of alterations in venous flow to the thorax, as has been argued by some, because such a hypothesis would not explain the immediate decrease in the pulse following inspiration after a long period of apnea.¹⁵ The fact that the changes in pulse size do not coincide with the variations in diastolic pressure suggests that the changes in the pulse amplitude are not due to variations in the capacity of the aorta.

The changes in venous flow to the left ventricle can best be attributed, we believe, to an alteration in the capacity of the pulmonary veins. A change in the pressure around a tube which is open at both ends causes not only a like change in the pressure within, but also an opposite change in the caliber of the vessel. These changes are not proportional, however, but their extent depends on the character of the vessel wall. During respiration one would therefore expect a variation in the size of the pulmonary vessels, particularly the veins. This was found to be true by de Jager,¹⁶ who demonstrated a decrease in the capacity of the pulmonary vessels during expiration and an increase during inspiration, the changes being much greater in the pulmonary veins than in the pulmonary arteries. As the pulmonary veins increase in size during inspiration, part of the blood passing through them is retained to fill the widened channels, and less reaches the left side of the heart. During expiration the pulmonary veins decrease in size and the blood that had been, so to speak, stored in them during inspiration now augments the venous flow to the heart. Respiration always has this effect, but it is only when it is greatly accentuated that enough alteration in the ventricular filling and discharge is obtained to cause a pulsus paradoxus.

According to this conception, the amount of change in intrapleural pressure is important, but much more important is the velocity with which the pressure varies. It is apparent that the amount of blood delivered to the left side of the heart during apnea is equal to the amount entering the pulmonary veins from the pulmonary capillaries. A discrepancy occurs only when the vessels are changing in caliber, and the degree of discrepancy will obviously depend on the rapidity of the alteration in the size of the vessels or, in other words, on the velocity with which the intrapleural pressure is modified. This dependence of the changes in pulse size on the velocity of respiration has actually been found in our clinical cases, and an analysis of the animal experi-

15 The relationship found in Cheyne-Stokes breathing can be demonstrated readily by having a person hold his breath with the chest in midposition as long as possible and noting the pulse when he first inspires. It will be found that the pulse decreases in the beat that follows the beginning of inspiration.

16 De Jager, S. Arch f d ges Physiol 20: 426, 1879.

ments showed it to be true here also—as will be seen when one compares the effect of inspiration and expiration in Figure 7 A and 8 from this point of view.

The explanation suggested above seems to us to be the most logical account for the facts observed. None of the others which we have considered in the course of this study fit the facts so well.

III EXPERIMENTAL OBSERVATIONS PERTAINING TO THE PULSUS PARADOXUS IN PERICARDIAL EFFUSIONS

The pulsus paradoxus as observed in clinical cases with pericardial effusions was discussed in the preceding paper.¹ A feature of the paradoxical pulse under these circumstances was the fact that it was not accompanied by any extraordinary efforts of breathing. It seemed rather remarkable that patients with ordinary tranquil respiration should show such a respiratory variation in the size of the pulse. Consequently, it was apparent that some factor other than an increased intrapleural pressure variation was the cause of the pulse phenomenon. Pericardial effusions were accordingly reproduced in animals in order to determine the nature of this factor.

Pericardial effusions have been used to study the circulation in a variety of ways by a number of observers. Cannon and Cattell,¹⁷ for instance, used it in their researches on shock. Hoke⁴ observed a variation in the size of the pulse when fluid was injected into the pericardium of a rabbit. Starling,¹⁸ on injecting oil into the pericardium, found among other things that the arterial pressure fell and the venous pressure rose. Lewis,¹⁹ using small cats, noted that a slight rise in pericardial pressure caused a disproportionate fall in arterial pressure. Although the methods used by these investigators were satisfactory for their purposes, they did not faithfully reproduce all the conditions found in clinical cases of pericardial effusion.

Method.—A technic was developed by which an infusion could be produced in a naturally breathing animal with closed chest. Dogs were anesthetized as before, a pleural cannula was inserted into the pleural sac, and the inspiratory and expiratory pressures were noted in the manner already indicated. Tracheotomy was then performed and artificial respiration instituted. A 4-inch (10 cm) vertical incision was made over the lower part of the left side of the chest in the parasternal line and the ribs exposed. Two or three ribs were then resected for a distance of 3 inches (7.5 cm) and the parietal pleura incised. A window was thus made into the pleural cavity. The parietal pericardium near the cardiac

17 Cannon, W. B., and Cattell, M. K. Experimental Traumatic Shock, Critical Level in a Falling Blood Pressure, *Arch. Surg.* 4: 300 (March) 1922.

18 Starling, E. H. *Lancet* 1: 652, 1897.

19 Lewis, T. *J. Physiol.* 37: 233, 1908.

apex which appeared medial to the opening was next grasped with several hemostats and brought out through the window. A half inch (12.5 cm) incision was now made in the pericardium and a loose silk purse-string suture run around the opening. Into this the flanged end of a specially constructed brass cannula was inserted, the purse-string suture was tightened and tied and the collar screwed down. A non-leakable connection was made in this way, which was confirmed by a postmortem examination on every preparation.

The cannula was connected to a manometer by means of rubber tubing. After the pericardium was replaced, this tubing was brought out through the hole in the chest. Enough tubing was left in the chest to permit unhampered movement of the heart. The window in the chest was closed by stitching the ribs, muscle flaps and skin in place. Several pieces of petrolatum soaked gauze were inserted between the various layers in order to make the closure air tight.

The lungs were markedly inflated so as to obliterate the pleural space and expel the air in it through the pleural cannula which was then connected to a tambour (or segment capsule) and manometer as described before. The intrapleural pressure was again read after the artificial respiration was stopped and natural breathing resumed. It was our experience that when the wound closure was air-tight the intrapleural pressure readings were approximately the same as before the operation.

In the early experiments oil (bland paraffin) was injected into the pericardium by means of a T-tube inserted into the tube connecting the pericardium to the manometer. In the later experiments, physiologic sodium chloride solution was used. The pericardial pressure was read in millimeters of oil or saline solution depending on which was utilized. The difference in specific gravity between the two was not great enough to require correction, at least for our purposes, the lower viscosity of the saline solution permitted more accurate readings of the variations in pressure, however. In some of the experiments the pericardial pressure was optically recorded with a fair degree of accuracy by connecting the top of the pericardial manometer to a segment capsule.

The pulse and respirations were recorded as before. Venous pressures were read directly by means of saline manometers, which were connected to sounds inserted into the external jugular veins. On the right side, the sound was inserted so that the opening in it was within the pericardium, that is, in the right auricle. The sound in the left innominate vein was placed just within the thorax, so that its open end was without the pericardium. The position of the sounds was of course confirmed at necropsy, and corrections were made for the zero level. As will be pointed out later, we were interested in simultaneous readings of the two pressures, so a device was constructed to permit this.

A stop cock was inserted in each circuit and so arranged as to be operated by a single lever. Thus, when a reading was desired at the end of inspiration (or expiration) it was obtained by turning the lever at the proper moment, thereby interrupting both circuits at the same time.

Effect of Experimental Pericardial Infusion on the Pulse.—The first effect noted on injecting fluid into the pericardium was a decrease in the size of the pulse and a fall in the blood pressure—mean, systolic and diastolic (Fig. 9), but the most striking change was the appearance of a pulsus paradoxus. The injection of fluid caused a waxing and waning in the pulse or markedly accentuated one already present (Figs. 9 and 10). The degree of these changes was found to be proportional to the pressure developed in the pericardial sac. Sometimes the paradoxical pulse appeared as soon as fluid was injected, at other times, only after a moderate degree of pressure was developed. Furthermore, the degree of the pulse variation increased as the sac was

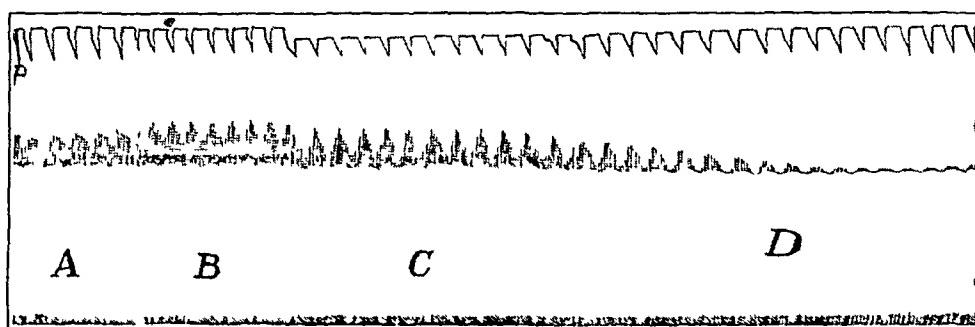


Fig. 9 (Exper. 306 C, C'')—Slow smoked drum tracing showing the effect of pericardial infusion on the carotid pulse and intrapleural pressure. Segment A, control; Segments B, C and D, various stages during infusion of oil. Records obtained as in Figure 7 A.

	Cc of Oil in Pericardium	Intrapleural Pressure (in Mm of Saline)			Mean Pericardial Pressure (in Mm of Oil)
		Inspiration, Mm	Expiration, Mm	Variation, Mm	
End of A	0	-120	-70	50	0
B	150	-110	-80	30	+100
End of C	180	-110	-70	40	+160
Middle of D	195	-90	-60	30	+300

distended with fluid until the pulse became very small, when it became less conspicuous (Fig. 9).²⁰

Time Relation of the Changes in Pulse Size to the Phases of Respiration.—A careful analysis of our records, typical examples of which are shown in Figures 10 and 11 A and B, reveals a time relationship similar to that found in exaggerated breathing. The change in

²⁰ In addition, there was less fluctuation in diastolic pressure as compared with the pulse in exaggerated breath (compare Figs. 10 and 7 A).

pulse size always occurred in the first or second beat after the onset of the respiratory phase, regardless of the fact that this series had a wide range of respiratory and heart rates. This time relationship indicates that the pulsus paradoxus in pericardial effusions is due directly to alterations in the venous return to the left heart in that it follows in the same period as the response to manipulation of the pulmonary vessels (note Fig. 5).

Nature of the Mechanism by Which the Venous Flow to the Left Side of the Heart Is Altered.—The mechanism producing the pulsus paradoxus in pericardial effusion resembles that in exaggerated breathing in that the pulse in this condition is also primarily due to the effect of intrapleural pressure variations, since it does not persist when the pleural pressure variations are eliminated. The mechanisms differ, however, in that a pulsus paradoxus occurs in pericardial effusions even

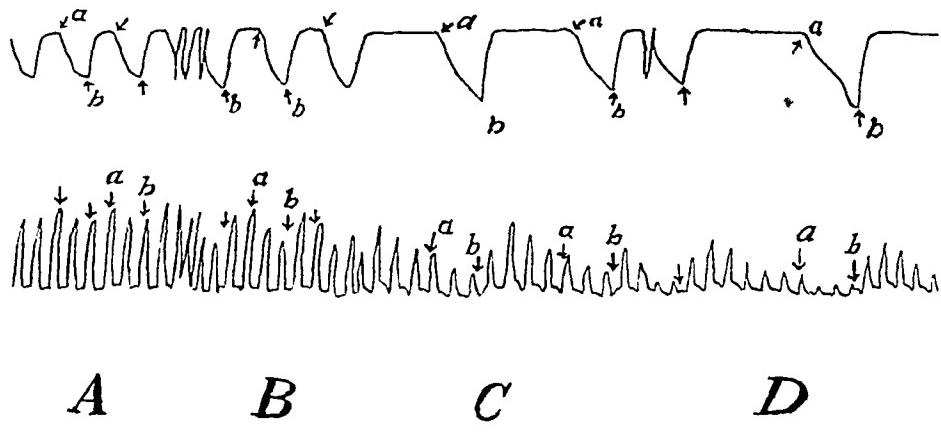


Fig. 10 (Exper 302 H, J, L and M) Smoked drum record showing the effect of pericardial infusion on the carotid pulse and intrapleural pressure. Curves recorded as in preceding figure, *a*, beginning of inspiration, *b*, beginning of expiration. Segment *A*, control, segments *B* to *D*, various stages during infusion of oil.

	Amount of Oil in Pericardium, Mean Pressure in Pericardium	
	C _t	Mm of Oil
A	0	0
B	40	+90
C	80	+200
D	100	+250

when the depth of breathing is not exaggerated. Reference to Figures 9 and 10 will show this to be the case, as will the data presented on this point in Tables 1 and 3. It was our experience that ordinarily the depth of breathing (as indicated by the amount of variation in the intrapleural pressure) was not increased by injection of fluid in the pericardium except when the circulation was so interfered with as to cause partial asphyxia. An example of this is shown in the upper tracing in

TABLE 1—Effect of Pericardial Effusion on Pressure in the Pleural and Pericardial Cavities

1 Experiment	2 Amount of Fluid in Peri- cardium	3 Intrapleural Pressure			5 Variation	6 Intrapericardial Pressure			8 Variation
		Inspira- tion	Expira- tion	Variation		Inspira- tion	Expira- tion		
317-1	0*	-50 †	-28 †	22 †	-25 †	-10 †	15 †		
317-5	0	-34	-16	18	-30	-12	18		
317-8	0	-36	-18	18	-30	-14	16		
317-2	25	-50	-20	30	+5	+24	19		
317-3	75	-40	-20	20	+54	+60	6		
317-6	75	-36	-16	20	+62	+71	9		
317-7	100	-36	-12	24	-150	+160	10		
317-4	105	-40	-20	20	+100	+165	5		

* Cubic centimeters of saline solution injected

† Millimeters of saline solution

TABLE 2—Effect of Varying the Pressure About the Excised Pericardium on the Pressure Within It

	Pressure Around Peri- cardium, Mm †	Pressure Within Pericardium					
		When Containing No Fluid, Mm †	When Distended with Fluid to Varying Degrees				Mm †
			Mm †	Mm †	Mm †	Mm †	
A, before partial vacuum produced		0	0	+230	+475	+775	+990
A', after vacuum released		0	0	+190	+435	+745	+970
B, on producing partial vacuum	-200	-195	+90	-365	+705	+950	
C, average difference of pressure*	200	195	120	90	55	30	

† Of saline solution

$$* \text{ Obtained by formula } C = \frac{(A + A')}{2} - B$$

TABLE 3—Effect of Pericardial Effusion on the Venous Pressure

1 Experiment	2 Amount of Saline Solution in Peri- cardium, C.c.	3 Pressure in Pleural Cavity, Mm of Saline Solution			6 Pressure in Pericardium, Mm of Saline Solution			9 Intravenous Pressure in Innominate Vein, Mm of Saline Solution			12 Right Intra- auricular Pressure, Mm of Saline Solution		
		Inspiration	Expiration	Variation	Inspiration	Expiration	Variation	Inspiration	Expiration	Variation	Inspiration	Expiration	Variation
319-1	10	-70	-40	30	-50	-25	25	-1	-5	6	-18	-12	6
319-2	0	-70	-40	30	-50	-20	30	-1	-2	5	-20	-15	5
319-3	0	-76	-40	36	-45	-20	25	-1	-2	7	-20	-15	5
319-4	60	-72	-40	32	-5	+12	17	+14	+18	4	-1	+5	4
319-5	120	-70	-40	30	+50	+60	10	+60	+64	4	+63	+65	2
319-6	120	-70	-40	30	+50	+60	10	+59	+64	5	+63	+65	2
319-8*	0	-82	-44	38	-50	-20	20				-10	-10	20
319-9	115	-80	-40	40	+100	+110	10				+112	+120	8
319-10	115	-72	-40	32	+104	+112	8				+115	+122	7
319-11	115	-70	-40	30	+99	+105	6				+115	+120	5

* Saline injected intravenously in interim

Figure 9, where it will be noted that the breathing is only increased in the last part of the tracing. We can only conclude from these observations that the presence of fluid in the pericardium introduces a factor which in some way amplifies the effects of intrapleural pressure. This factor we found to be intimately associated with the intrapericardial pressure.

The Pressure in the Pericardial Sac.—We found that the elevation of intrapericardial pressure was not proportional to the amount of fluid injected. If the amount of fluid in the pericardium was increased in an arithmetic progression, the pressure was found to increase more or less in a geometric progression (note data given in Table 1 and legend beneath Figure 9). Although the pressure level in the pericardium increases as fluid is injected, that in the pleural sac remains practically unaltered because of the interposition of the parietal pericardium between these two spaces. For example, in a marked case the pressure in the pericardium rose 300 mm., whereas that in the pleural cavity increased but 20 mm. (note legend beneath Figure 9).

In addition, a striking change was noted in the respiratory pressure variations in the pericardial sac. Normally the intrapleural pressure variations are transmitted into the pericardium. However, when fluid is injected the influence of the pleural pressure variation on the pericardial pressure is diminished. These facts are apparent on analyzing the data in Tables 1 (Columns 5 and 8) and 3 (Columns 8 and 14). A marked case may be cited. The injection of oil into the pericardium of an animal caused in this instance an elevation of 100 mm. in pericardial pressure and the appearance of a pulsus paradoxus. It was found that while the intrapleural pressure showed a fluctuation of 130 mm., the pericardial pressure showed only a respiratory variation of 10 mm.²¹

The findings in this connection were somewhat unexpected, and therefore an attempt was made to verify them in other ways. Records of the pericardial pressure were obtained optically, simultaneously with the intrapleural pressure. Although the records are slightly distorted, they are accurate enough to show definitely the decrease in the amount of pressure variation. Thus, in Figure 12, which is an example of such a record, segment *A* is the control and *B* the curve when the sac was distended with saline solution. The excursion of the pericardial pressure (upper curve) is greater than the excursion of the intrapleural pressure (lower curve) in segment *A* due to the more sensitive membrane used to record pericardial pressure. It will be seen that the pericardial curve is much smaller in *B* than in *A*, although the intrapleural curve is as large as before.

²¹ Although part of this difference might be attributed to the viscosity of the oil, this played but a minor rôle as like differences were obtained when saline solution was used.

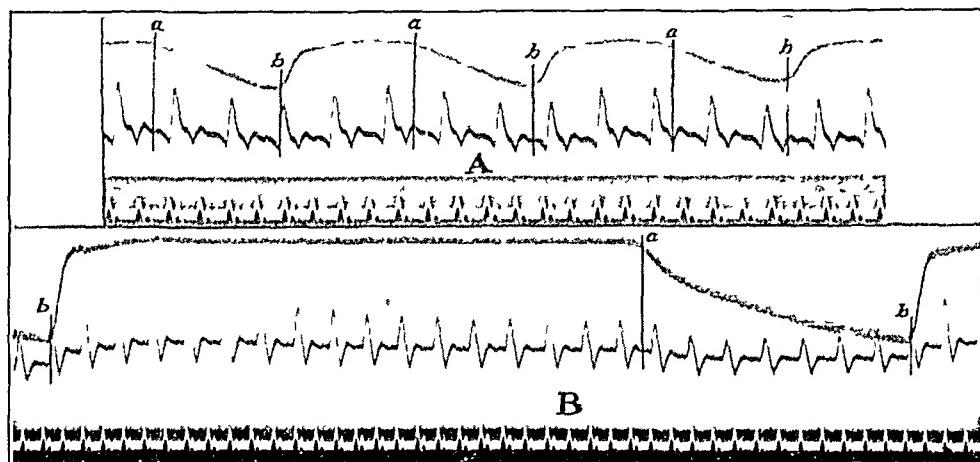


Fig 11.—Optical records obtained while pericardial sac was distended with saline solution, showing the time relation of the pulse changes as described in text. The lower curve indicates the carotid pulse obtained with the plethysmograph, upper curve, intrapleural pressure

Segment A, Exper 315-4 Vagi intact, 90 cc of oil in pericardium, pressure in pericardium varied 9 mm (from + 134 to + 125 mm of saline), intrapleural pressure varied 20 mm (from -20 mm to -40 mm of saline)

Segment B, Exper 316-1 Both vagi sectioned, 100 cc of saline in pericardium, pericardial pressure not obtained, intrapleural pressure varied 50 mm (from 0 to -50 mm of saline)

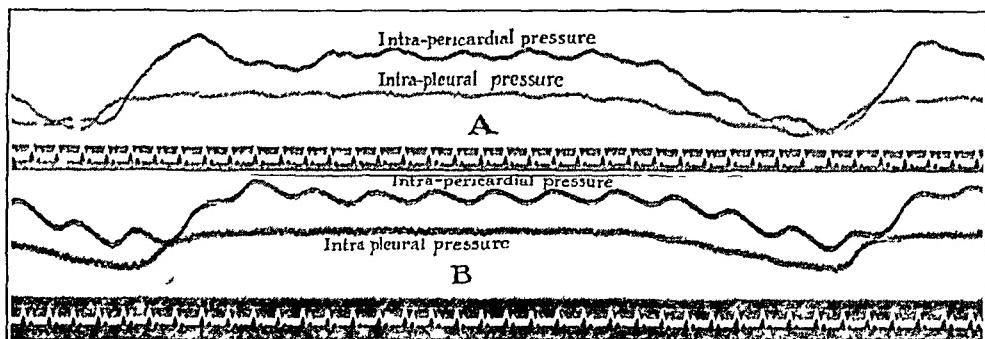


Fig 12 (Exper 315-10, 15)—Simultaneous optical records of intrapleural and pericardial pressures. A, control, no saline in pericardium, B, 70 cc of saline in pericardium Time in tenths of a second

	Intrapleural Pressure (in Mm of Saline)			Intrapericardial Pressure (in Mm of Saline)		
	Inspiration, Mm	Expiration, Mm	Variation, Mm	Inspiration, Mm	Expiration, Mm	Variation, Mm
A	-60	-24	36	-60	-25	35
B	-56	-16	40	+36	+56	20

As a further check, observations were also made on the excised pericardial sac where conditions could be more readily controlled. The pericardium was dissected out with the pericardial cannula in place. The various vessels were tied as they emerged from the pericardium except the inferior vena cava and one of the pulmonary veins. The heart was distended by injecting saline solution through the latter vessels, after which they were tied. The preparation was then placed in a glass jar which could be sealed air tight. The cover of this jar had two holes, through one of which the tubing from the pericardial fistula was brought out and connected as in the living animal experiments. The other hole which communicated with the inside of the jar was connected to a manometer. A side tube was inserted in this connection, and through it the pressure in the jar was altered. The effect of changing the pressure in the jar on the pressure within the pericardial sac was observed both when the sac was undistended and also when it was distended with fluid.

The results, illustrated by a single experiment analyzed in Table 2, show that under normal conditions the changing pressures around the pericardial sac are transmitted without loss to the interior. However, when the sac is distended with fluid, the intrapericardial pressure changes are only from one-fourth to one-half as great as those on the outside. This is undoubtedly due to the relative inelasticity of the pericardium (Barnard²²) and the fact that it rapidly reaches the limit of its elasticity as more and more fluid is forced into it. Under such conditions, comparatively slight pressure variations—either such as occur during inspiration and expiration within the chest, or even such as were mechanically produced in our “jar preparation”—are unable to stretch or compress the rigid pericardium further. Physiologically, the pericardial contents become virtually extrathoracic.

Interpretation of the Pulsus Paradoxus in Pericardial Effusion.—With these facts established, it is possible for the first time to formulate a hypothesis which logically explains the paradoxical pulse in pericardial effusion. Normally, the variations of intrapleural pressure during expiration and inspiration are transmitted without loss through the pericardium to the chambers of the heart. Consequently, the fall of intrathoracic pressure produced during inspiration affects the pressures within the auricles and ventricles about as much as the pressure in the entering extrapericardial veins. It follows that the effective difference in pressure between the veins and the heart is at least not greatly altered by the act of inspiration, and the systolic discharge is practically unaffected by this factor.

When, on the other hand, the limit of distensibility is more nearly approached by the pressure of fluid within the sac, the respiratory variations of intrathoracic pressure cannot affect intracardiac pressures as much as those in the entering veins. For example, inspiration will cause a smaller pressure fall within the auricle than within the entering veins, making the pressure gradient between these two points less in inspiration than during expiration. This must necessarily result in a reduced filling of the heart and a reduced discharge of those beats which come during inspiration, thus explaining the production of a paradoxical pulse even though a normal depth of breathing is maintained. In Figure 13, an attempt is made to express this conception graphically. Of course, only the trend of the pressure changes can be shown. If the shaded area represents the gradient of pressure between

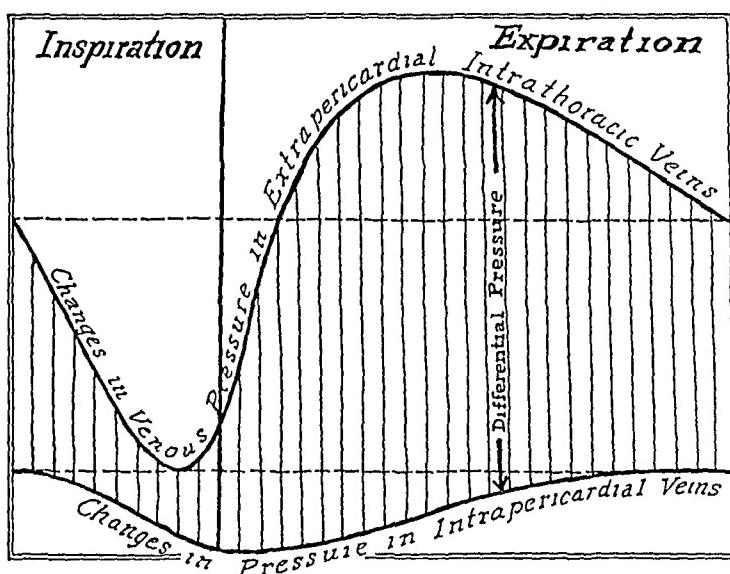


Fig 13.—Diagram showing variations of venous pressure gradient (differential pressure) during respiration when pericardial sac is distended with fluid

veins and auricle at different moments of the respiratory cycle, and it is recalled that the pressure difference determines ventricular filling and discharge as well as pulse amplitude, it should be clear how the waxing and waning of the pulse can be produced by pericardial effusion.

Experimental Proof of the Validity of This Hypothesis—While this hypothesis adequately explains the production of the paradoxical pulse in accord with experimental facts, it would go far toward greater surety if it could be shown that such pressure differences as are postulated by this conception actually obtained in the pulmonary veins and left side of the heart. Experimentally, this is far more difficult and probably no more decisive than similar observations on pressures in the right side of the heart and its entering veins. A study of the pressures in the superior vena cava and auricle was therefore made in naturally

breathing animals. Two sounds were inserted into the jugular veins so that their ends rested in the right auricle and entering veins as confirmed by postmortem examination. These were connected to U-shaped saline manometers on which accurate readings could be made. Provision was also made for flooding the cannulae periodically and so keeping them free from clots.

Two successful experiments were carried out. The results of one of these are tabulated in Table 3. The data show (1) that the introduction of fluid into the pericardial sac elevates the average pressures both in the right auricle and entering veins, and (2) that the respiratory variations of intra-auricular pressure decrease while the pressure variations in the entering veins remain unaltered. In other words, the pressure difference between the auricle and the entering veins becomes less during inspiration than during expiration.

For example, normally the venous pressure decreased from 6 to 7 mm during inspiration, while intra-auricular pressure decreased from 5 to 6 mm. After injecting 60 c.c. of saline solution into the pericardial sac, the pressure variations in both vein and auricle were 4 mm. After introducing 120 c.c. of saline solution, the venous pressure decreased from 4 to 5 mm during inspiration, while intra-auricular pressure fell only 2 mm. At this time a distinct paradoxical pulse could be palpated and recorded.

SUMMARY

The results of animal experiments carried out in order to elucidate the causes of pulsus paradoxus as found in clinical cases may be summarized as follows:

1. Mechanical compression of the aorta produces an immediate effect on the pulse amplitude, compression of the pulmonary veins causes a decrease within one or two beats, compression of the venae cavae, however, causes no effect on pulse amplitude for three or four beats. These time relations are of paramount importance in locating the influence that is responsible for a similar reduction in pulse amplitude during inspiration.

2. Traction exerted anywhere on the pericardial structures may produce a pulsus paradoxus, the presence and degree of which depend on the tension exerted rather than on the location of the "adhesions." Time relations show that such a pulsus paradoxus is always the direct or indirect result of partial occlusion of the pulmonary vessels, the aorta, or both, and never due to compression of the venae cavae.

3. Augmented breathing experimentally produced in a variety of ways causes a waxing and waning of the pulse during expiration and inspiration. Details of experiments are given showing that this is due to increased variations in intrapleural pressure and not to traction effects. The greater the depth and velocity of these pressure changes,

the greater the effect on the pulse. Time relations show that the effect is exerted on the volume flow into the left side of the heart, and this we interpret as being due to the changing capacity of the pulmonary veins.

4 In artificial pericardial effusions experimentally produced, a pulsus paradoxus appears without change in the depth of breathing, thus simulating the clinical condition. Experiments are detailed showing that the pulse amplitude is decreased in the first or second beat after the onset of inspiration. This eliminates the possibilities that the pulsus paradoxus is directly due to an effect of inspiration on the volume of either the aorta or venae cavae, and shows that it is occasioned by the effect of variations in intrapleural pressure on the volume flow to the left side of the heart.

5 The facts established by experiments, notably (a) that intra-pericardial pressure varies less during respiration when the sac is distended with fluid than it does normally, and (b) that with a distended sac intra-auricular pressure changes less during each respiratory cycle than the pressure in the entering veins, favor the following explanation of the paradoxical pulse during pericardial effusion.

With the pericardium distended with fluid, not only is the flow of blood into the heart impeded, but the inflow also varies during inspiration and expiration, owing to the fact that the respiratory variations of intrathoracic pressure do not affect the intrapericardial and intracardiac pressures as much as those in the entering veins. This causes a smaller difference of pressure between the veins and heart during inspiration and allows less filling of each ventricle. Consequently, a paradoxical pulse probably appears in both the pulmonary and systemic circuits, but obviously the arterial pulsus paradoxus is due to the impaired inflow into the left ventricle.

THE ORIGIN OF URINARY AMMONIA *

SECOND PAPER

I M RABINOWITCH, MD

MONTREAL

Of the enormous amount of work done concerning the concentration of ionized hydrogen in the body fluids, much is of more than abstract interest from the clinical point of view. The recognized fact that even in disease the true reaction of the blood varies within narrow limits has led to much study of the possible factors controlling this phenomenon. It is from work on this phase of the subject that observations primarily of interest to the physical chemist only have now become of interest and importance to the clinician.

In this communication, we are concerned only with the part that the kidneys play in the regulation of the body neutrality. The literature is enormous, and recently¹ excellent reviews have appeared on the subject. Experimentally, an acidosis may be produced in man by proper changes in diet, such as restriction of carbohydrates or salts. Even under normal conditions of diet there is always a tendency toward the production of an acidosis. Thus, in the normal food of man, the acid radicals present are in excess of the basic ones. Acid formation is therefore in excess of base formation. This excess of acid radicals is eliminated by the lungs and the kidneys. The value of the study of the urinary acidity and the factors which modify it are thus apparent. The reaction of the blood varies within narrow limits, even in disease, and is nearly always alkaline (p_H 7.4). The reaction of the urine has a wider limit of variation and is nearly always acid. In normal persons² the urine may be as much as 400 or more times as acid (p_H 4.82) as the blood (p_H 7.45) or may be just slightly more alkaline (p_H 7.46). Though this wide variation may be noted in individual studies, in a statistical sense, under general conditions of diet and activity, the average acidity is fairly constant, p_H 6.03, or about 13 times more acid than blood. In a thorough study of the factors which account for the wide fluctuations in the acidity of normal and pathologic urines, Henderson and Palmer² have shown that such fluctuations are charac-

* From the Department of Metabolism, Montreal General Hospital.

1 Van Slyke, D. D. The Carbon Dioxide Carriers of the Blood, *Physiol Rev* **1** 141 (Jan.) 1921. Wilson, D. W. Neutrality Regulation in the Body, *Physiol Rev* **3** 295 (July) 1923.

2 Henderson, L. J., and Palmer, W. W. On the Intensity of Urinary Acidity in Normal and Pathological Conditions, *J Biol Chem* **13** 393 1912-1913. On the Several Factors of Acid Excretion, *Ibid* **17** 305, 1914. On the Several Factors of Acid Excretion in Nephritis, *Ibid* **21** 37, 1915.

teristic of a phosphate mixture containing phosphoric acid and base. The base varies from the amount necessary to form monobasic to that necessary to form dibasic phosphate. A further study of the acidity and excretion of titratable acid and ammonia was made by the same authors in urines of normal and nephritic persons. They observed an increase in the intensity of the acidity of the urine in nephritis accompanied by a diminished elimination of total acid (titratable acid plus ammonia). In cardiorenal disease the average acidity (p_H 5.33) was over 100 times greater than that of the blood. For the first time they recorded a condition of acidosis accompanied by a diminished excretion of ammonia. Judging from the scanty literature on the subject, the practical clinical significance of these important observations appears to have been overlooked.

In 1921, Nash and Benedict³ reviewed the literature and made a fundamental observation concerning the origin of urinary ammonia. The findings of these authors renew interest in the study of the excretion of the titratable acid and ammonia in the urine. Not only has the clinical value of this test become enhanced, but an additional interpretation is attached to the results. Briefly, because of the low values accepted for the concentration of ammonia in the blood, it appeared difficult to explain the amounts of ammonia at times found in urine. By calculating the amount of ammonia which could pass through the kidneys each day, it is found that a sufficient amount could not pass through to account for the amount found in the urine. As a result of animal experimentation, these authors concluded that the urinary ammonia must be formed within the kidneys. Further animal experiments by the same authors⁴ seemed to substantiate this view. Studies made by Russel⁵ on advanced renal disease show low values for blood ammonia and lend support to the Nash and Benedict hypothesis. The part that ammonia may play in the regulation of the reaction of body fluids is readily appreciated from certain observations on the alkali binding capacity of phosphoric acid.¹ At p_H 4.8, a urine reaction, one molecule of phosphoric acid is combined with less than one molecule of base as acid sodium phosphate. At a p_H 7.45, the reaction of the blood, one molecule of phosphoric acid is combined with about 18 molecules of base. Thus in the excretion of one molecule of phosphoric acid, nearly one molecule of base may be retained within the body. Another observation is that one molecule of ammonia represents the saving

³ Nash, R. P., Jr., and Benedict, S. R. The Ammonia Content of the Blood and Its Bearing on the Mechanism of Acid Neutralization in the Animal Organism, *J. Biol. Chem.* **48** 463, 1921.

⁴ Nash, T. P., Jr., and Benedict, S. R. Note on the Ammonia Content of the Blood, *J. Biol. Chem.* **51** 183, 1922.

⁵ Russel, D. S. The Ammonia Content of the Blood in Nephritis. *Biochem. 17* 72, 1923.

of one molecule of base. The importance of the observation that the kidneys are the site of ammonia thus becomes apparent. In the presence of a kidney lesion associated with a defective mechanism for the production of ammonia, the acids formed either in health or in disease in the absence of sufficient ammonia must call on the reserve bases of the body. If the kidneys are the site of ammonia formation, the part played by them in the regulation of the reaction of the body fluids, as pointed out by Nash and Benedict, becomes clear. An acidosis may be produced either when the rate of acid production is greater than the rate of ammonia formation, as may occur in diabetes, or even under conditions of a normal amount of acid production, if the kidneys have lost the function of ammonia formation, as in nephritis.

Since the publication of the experimental work of Nash and Benedict, observations on the blood and urinary ammonia in diabetic and nephritic patients have been made in this hospital, and the estimation of the titratable acid and ammonia in the urine of diabetic patients has been practically a daily routine in all cases. The published data⁶ in which the blood and urine ammonia values are correlated give clinical confirmation to the experimental work.

A study of the data obtained on the titratable acid and ammonia, which is recorded here, emphasizes the clinical importance of such determinations when considered from the point of view that the kidneys are the site of ammonia formation. Observations were made in 1,422 instances, including 112 cases of diabetes. The data are recorded below. The diabetic cases are divided into four groups, as follows:

Group 1 Cases with no nephritis (no albumin, no casts) and no ketosis

Group 2 Cases with no nephritis but with ketosis

Group 3 Cases with nephritis but no ketosis

Group 4 Cases with nephritis with ketosis

The other routine data concerning blood and urine sugar, etc., are omitted as they have no direct bearing on the present discussion. The work done in which the clinical picture and the results of the various renal function tests are correlated with the amount of ammonia excreted form part of a separate communication. The object in this article is only to show, in a statistical sense, the effect of nephritis on the excretion of ammonia and also an observation which does not appear to have been hitherto recorded in diabetes—the quantitative relation between acid and ammonia production.

It need hardly be stated that all values were obtained from complete twenty-four hour specimens of urine, collected and preserved

⁶ Rabinowitch, I. M. The Origin of Urinary Ammonia, Canad. M. A. J., October 1923.

(ice and toluene) under standard conditions for metabolism work. The acid was titrated to p_H 8.5, using phenolphthalein as the indicator. The data are recorded in the tables. It will be noted that the same hospital number in some instances appears in two tables. This was done with the object of separating the urinary ammonia values in the four groups mentioned above, thus showing the effect of acid production on ammonia formation. It is generally recognized that a glance at any table in which are recorded the values of the daily excretion of total acid (titratable acid plus ammonia) shows the difficulty under which one must observe the relation, if there be any, between the production of acids and the formation of ammonia. It appears that since the reaction of the blood is fairly constant, the factors controlling the reaction must

TABLE 1.—*Urinary Ammonia in Normal Persons and in Persons with Nephritis*

Normal			Nephritic					
Case No	No of Determinations	Ammonia, Grams per Liter Acid	Case No	No of Determinations	Ammonia, Grams per Liter Acid	Case No	No of Determinations	Ammonia, Grams per Liter Acid
1	12	0.94	1	4	0.33	23	3	0.80
2	7	0.85	2	5	0.37	24	7	0.86
3	5	1.07	3	7	0.43	25	2	0.85
4	8	0.90	4	2	0.45	26	3	0.85
5	8	1.00	5	2	0.55	27	7	0.85
6	11	0.86	6	5	0.57	28	5	0.81
7	8	1.06	7	4	0.60	29	5	0.86
8	8	1.13	8	9	0.58	30	2	0.86
9	6	1.14	9	5	0.57	31	28	0.88
10	10	0.97	10	5	0.59	32	5	0.91
11	5	0.95	11	18	0.61	33	9	0.93
12	9	1.01	12	19	0.64	34	11	0.93
13	6	0.78	13	10	0.65	35	7	0.97
14	7	1.04	14	4	0.61	36	3	0.95
15	6	1.08	15	3	0.68	37	5	0.93
16	7	0.89	16	2	0.69	38	5	0.93
Average			17	5	0.76	39	10	1.50
			18	11	0.77	40	26	1.03
			19	2	0.81	41	6	1.01
			20	4	0.81	42	3	1.05
			21	6	0.82	43	9	1.04
			22	11	0.84	44	7	1.07
Average								

TABLE 2.—*Urinary Ammonia in Persons with Diabetes Mellitus with No Albuminuria and No Ketosis*

Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid	Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid
2867	3	0.90	3515	2	0.87
4158	2	0.97	2994	1	1.00
5831	7	1.34	977	1	0.95
274	6	0.97	844	11	0.93
5135	8	1.10	892	6	0.97
5913	7	1.06	4126	5	0.85
6109	7	0.87	2846	8	0.83
527	1	0.91	1154	3	1.05
819	6	1.07	5529	5	1.01
2783	1	1.20	456	7	0.99
2070	1	0.93	2202	7	0.86
6038	3	0.85	2601	5	0.88
6155	3	1.10	2673	5	0.83
3022	3	0.84	1604	1	0.81
3593	6	1.01	2682	1	0.86
2363	6	1.28	3531	3	0.84
1438	2	0.78	3283	4	0.81
Average					0.96

TABLE 3.—*Urinary Ammonia in Persons with Diabetes Mellitus and Ketosis with No Albuminuria*

Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid	Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid
3593	19	1.41	818	2	0.79
274	1	1.32	844	4	1.02
1157	4	1.04	1481	10	1.07
2867	6	1.12	3470	9	1.09
3002	14	1.06	892	8	0.93
527	18	1.08	2846	2	0.96
5831	10	1.38	1154	6	1.01
4691	10	1.13	2601	15	1.12
4168	12	1.05	2092	4	0.73
1438	7	0.90	2597	15	1.29
4965	18	1.29	4487	1	1.26
5157	10	1.22	1522	7	1.12
6038	4	0.80	6109	9	1.17
6155	13	1.18	3561	5	0.83
807	20	1.13	3593	11	1.39
2783	9	1.13	2864	1	1.07
Average					1.09

TABLE 4.—*Urinary Ammonia in Persons with Diabetes Mellitus with Albuminuria but No Ketosis*

Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid	Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid
498	7	0.77	5500	7	0.77
1193	5	0.66	5908	9	0.74
1157	8	0.76	1402	10	0.62
1213	11	0.67	783	5	0.86
1489	10	0.84	2951	5	0.55
1749	1	0.74	2968	2	0.90
3352	7	0.84	2602	2	0.81
479	8	0.77	940	9	0.55
3844	4	0.73	3501	7	0.76
3889	7	0.83	2423	4	0.66
57	1	0.69	2917	4	0.77
352	9	0.68	679	10	0.60
	1	0.77	2302	4	0.75
1739	2	0.59	5649	1	0.50
1753	8	0.71	3663	7	0.83
1980	6	0.61	2065	5	0.63
2455	15	1.03	1522	4	0.66
2365	25	0.84	2284	10	0.77
479	6	0.80	1022	4	1.09
4102	1	0.94	6136	4	1.00
4172	11	0.93	3006	3	0.74
3075	9	0.85	5961	10	0.61
3614	6	1.05	6397	4	1.04
Average					0.75

TABLE 5.—*Urinary Ammonia in Persons with Diabetes Mellitus with Albuminuria and Ketosis*

Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid	Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid
1022	3	1.14	2951	4	0.66
1193	1	0.59	2602	15	0.93
1213	1	0.58	2423	4	0.72
1157	1	0.74	1255	6	0.71
1489	1	0.89	1207	18	0.87
6232	13	0.84	4559	6	0.55
479	1	0.82	1200	5	0.67
57	6	0.99	1040	6	0.81
2365	4	0.86	2302	5	0.83
1739	11	0.96	5649	14	0.98
1753	1	0.68	2070	3	0.72
498	2	0.96	2284	10	0.81
4102	5	0.90	6297	7	1.05
3006	2	0.51	3501	5	0.88
6136	3	0.66	1837	18	1.08
3455	10	0.89	2968	3	1.05
3655	12	0.88	3401	21	0.89
2994	7	0.83	6421	15	1.31
2682	13	0.94			
Average					0.84

normal persons represent 122 observations in sixteen subjects. Those for nephritic persons represent 311 observations in forty-four subjects, and those for diabetic persons represent 989 observations in 112 subjects. Excretion of urinary ammonia in terms of grams per liter of total acid (titratable acid plus ammonia) excreted is recorded. Thus in recalculating the values of Henderson and Palmer's work the cubic centimeter of ammonia was multiplied by the common factor 0.0017, the value of 1 c.c. tenth normal ammonia in grams.

RESULTS

Table 1, in which the data of normal and nephritic persons are recorded, strikingly demonstrates that the production of ammonia per liter of acid excreted is greater in normal than in nephritic persons. In normal persons, the formation of ammonia is approximately 1 gm per liter of total acid, whereas in nephritic persons it may be much less. Although diabetic persons can hardly be regarded as normal, from the point of view of the presence or absence of renal lesions, it will be noted in Table 2 that in diabetic patients with no renal lesions the response of ammonia formation to acid production closely approximates the normal values found in Henderson and Palmer's case, the averages being 0.98 and 0.96 gm of ammonia per liter, respectively. In the case of diabetic patients with ketosis and no nephritis (Table 3), the response of ammonia formation differs little from that of diabetic patients without ketosis, the average being slightly increased, 1.09 gm per liter. An observation made was that though the average for all values differs slightly in different persons, the different values found daily differ still less in the same person. In Tables 4 and 5, in which are recorded the data of diabetic persons with renal lesions, the average values are lower than in diabetic persons without renal lesions. It is apparent that some individual averages will resemble those of normal persons, since it has been frequently demonstrated that anatomic and functional integrity are not synonymous terms so far as nephritis is concerned. In spite of these normal values in isolated cases, the average is lower than in normal persons. An immediate clinical value may be attached to these data. The general clinical experience is that diabetic persons with nephritis are more susceptible to an acidosis than those with no nephritis, assuming other conditions, obesity, etc., as being constant. This in a great part is attributed to the vulnerability of the kidneys. The value of the estimation of the titratable acid plus ammonia and the grams of ammonia per liter of acid thus becomes enhanced. If the previously published data concerning the correlated values of blood and urine ammonia are considered, those recorded here further strengthen the view that the kidneys are the site of the formation of the urinary ammonia.

COMPARATIVE RESULTS OF COLLOIDAL GOLD AND COLLOIDAL MASTIC TESTS

AN ANALYSIS OF ONE THOUSAND SEVEN HUNDRED AND
SEVEN SPINAL FLUIDS¹

HARRY WASSERMANN, MD

BALTIMORE

It is now generally accepted that the physician who undertakes to treat syphilis is failing in his duty to the patient if he neglects routine studies of the spinal fluid. Studies carried out in this clinic¹ and elsewhere have shown that in addition to the procedures of cell count, globulin estimation and Wassermann reaction, there should be included the performance of a colloidal test such as the colloidal gold test of Lange which yields much information of diagnostic and possibly of prognostic import. Unfortunately, the preparation of the colloidal gold solution is so complex,² demanding absolute chemical cleanliness of all glassware and the use of triply distilled water, and the solution when prepared is so unstable that the use of this test is practically confined to large laboratories in centers of population.

Recent studies have shown that results analogous to those of the gold test may be obtained with colloidal suspensions of various gums or resins. Two of these have received particular attention, the colloidal benzoin reaction³ in France and the colloidal mastic test in Germany⁴ and in this country. In 1921, a paper was published from this clinic⁵ in which the results of the colloidal mastic reaction were compared with those of the colloidal gold test in 311 fluids. It was shown that there was fairly close parallelism between the two tests and that when agreement was lacking, the mastic seemed to be somewhat more delicate than the gold.

In view of the simplicity of preparation of the reagents used in the mastic test, it has seemed worth while to review our further results with

* From the Syphilis Department of the Medical Clinic, the Johns Hopkins Hospital

1 Moore, J E Studies in Asymptomatic Neurosyphilis II, Bull Johns Hopkins Hosp 33 231, 1922

2 Felton, L D A Study of the Specificity of the Colloidal Gold Reaction from a Physico-Chemical Standpoint, Trans Sect Path & Physiol A M A, 1917, p 73

3 Guillain, G , Laroche, G , and Lechelle, P La reaction du Benzoin colloidal et les reactions colloïdales du liquide céphalorachidien, Paris, Masson et Cie, 1922

4 Kafka, V Mastic Reaction in Cerebrospinal Fluid, Klin Wchnschr 2 829 (April) 1923

5 Keidel, A , and Moore, J E Comparative Results of Colloidal Mastic and Colloidal Gold Tests, Arch Neurol & Psychiat 6 163 (Aug) 1921

it in comparison with the gold test. This paper therefore sums up the results of the study of 1,707 spinal fluids in which both colloidal tests as well as the others enumerated were performed. This series includes the 311 cases published in our first paper.⁵ For the most part, the fluids are from patients in the various stages of syphilis although a number of other neurolologic conditions are included. The results of spinal fluid examinations have in each instance been compared with the clinical evidence of central nervous system disease, in an attempt to evaluate the comparative worth of gold and mastic reactions.

TECHNIC

For the sake of completeness, the technic employed, which is that recommended by Stanton,⁶ is repeated.

Ten grams of commercial gum mastic are dissolved in 100 cc of absolute alcohol, and the resultant cloudy fluid is filtered several times until a clear straw colored solution is obtained. This stock solution is

TABLE 1.—*Showing the Standards Employed in Reading the Colloidal Mastic Test, with Examples of Typical Curves**

Examples of Colloidal Tests

Dilutions of spinal fluid	Tube									
	1 4	1 8	1 16	1 32	1 64	1 128	1 256	1 512	1 1024	1 2048
Paretic zone	5	5	5	5	5	4	3	2	1	0
Syphilitic zone	0	1	1	2	3	3	1	0	0	0
Mastic "3"	3	3	2	1	0	0	0	0	0	0
Negative	2	2	1	0	0	0	0	0	0	0

* 0 indicates opalescence, no change; 1, milky fluid with no precipitation; 2, milky fluid with slight precipitation; 3, milky fluid with moderate precipitation; 4, cloudy fluid with almost complete precipitation; 5, clear fluid with complete precipitation.

kept in glass stoppered bottles at 100m temperature and does not deteriorate on standing. The emulsion is prepared with 1 cc of the stock solution added to 9 cc of absolute alcohol, which is then added, with gentle mixing, to 40 cc of once distilled water.

In setting up the test, ten small tubes are employed. To the first tube in the series are added 15 cc of a stock salt solution (99 cc of 125 per cent sodium chlorid solution plus 1 cc of 0.5 per cent potassium carbonate solution), and to each of the remaining tubes 1 cc is added. In the first tube, there is placed 0.5 cc of the spinal fluid to be tested. After mixing this dilution of spinal fluid, a titration is made throughout the series by transferring 1 cc from the first to the second tube, from the second to the third, etc., 1 cc being finally discarded from the last tube. Finally, 1 cc of the mastic emulsion is added to each tube. After mixing, the tubes are allowed to stand over night at room temperature,

6 Stanton, J. M.: Concerning the Colloidal Mastic Test, Arch Neurol & Psychiat 4:301 (Sept) 1920.

and the results are read in the morning. No special precautions regarding absolute cleanliness of glassware, such as are necessary for the gold test, need be observed.

The standards employed for reading results and typical readings of various types of abnormal fluids are shown in Table 1.

RESULTS

The comparative results of mastic and gold tests are summed up in Table 2. In 1,498 spinal fluids, or 87.7 per cent of the total number studied, there was agreement between the two tests. Both were negative in 1,260 fluids, while in 238 instances both were positive; in the majority of these cases the type of curve being the same. In only 12.3 per cent (209 cases) of the 1,707 fluids studied was there complete dis-

TABLE 2.—*A Summary of the Agreement Between Colloidal Gold and Mastic Tests, with an Analysis of Clinical and Laboratory Factors in Instances of Disagreement, Showing the Greater Delicacy of the Mastic Test*

Complete agreement (positive and negative)	1,446		
Partial agreement (degrees of positive)	52		
Total	1,498		
Disagreement (positive and negative)	209		
Analysis of the 209 in Which Disagreement Occurred			
	Diagnosis of Neurosyphilis Supported by		
	Total Cases	Clinical Evidence	Other Spinal Fluid Abnormalities
Gold positive, mastic negative	52	16 cases or 31%	22 cases or 42%
Mastic positive, gold negative	157	75 cases or 48%	97 cases or 62%

agreement between the two tests. This group includes 157 fluids which gave positive mastic curves when the gold was negative and fifty-two in which the reverse was true. It is further apparent from Table 2 that the clinical evidence and other abnormalities in the spinal fluid tend to confirm the value of the mastic test when disagreement between it and the gold test exists.

In Table 3 these results are subjected to closer analysis. It will be noted that the only type of abnormal curve common to the two tests is the paretic curve present in 161 fluids. In fifty-two instances the gold gave a syphilitic zone or paretic zone curve when the mastic test was negative, but this is more than counterbalanced by sixty-seven instances in which the mastic test gave a paretic curve while the gold was negative. Of the total number of fluids, 1,432 were obtained from syphilitic patients, either with or without clinical evidence of nervous system damage, and 275 were obtained from patients with other neurologic diseases in most of whom puncture was performed to rule

out neurosyphilis. As shown in the table, one or both colloidal tests gave abnormal results in twenty clinically nonsyphilitic patients. These include six patients with multiple sclerosis, five with epidemic (lethargic) encephalitis and three with brain or cord tumors, while the remainder comprise various neurologic disorders. The tendency of the three diseases named to show abnormal colloidal curves is well known.

In the first paper from this clinic, it was shown that a syphilitic zone mastic curve was uncommon, and some stress was laid on the probably equivalent value of the so-called "mastic 3" curve. It is of

TABLE 3—*Detailed Analysis of Agreement and Disagreement Between Colloidal Mastic and Colloidal Gold Curves*

Colloidal Tests	Total Cases	Diagnosis of Syphilis Without Clinical Evidence of Neurosyphilis	Diagnosis of Neurosyphilis Before Spinal Puncture	Cases for Diagnosis	Clinically Non syphilitic
Gold and mastic both negative	1,260	879	132	67	182
Gold and mastic both paretic	168	25	138	0	5
Gold paretic, mastic negative	18	9	9	0	0
Gold syphilitic, mastic negative	34	22	7	2	3
Gold syphilitic, mastic paretic	36	9	26	0	1
Gold negative, mastic paretic	67	23	40	0	4
Gold various, mastic "3"	117	64	44	4	5
Gold various, mastic syphilitic	7	3	2	0	2
Totals	1,707	1,034	398	73	202

TABLE 4—*Showing the Incidence of the Paretic Type of Colloidal Gold and Mastic Curves in Various Neurosyphilitic Diseases Before Treatment*

Type of Neurosyphilis	Total Cases	Gold					Mastic				
		Paretic	Syphilitic Zone	Negative	Percentage Paretic	Paretic	Syphilitic Zone	Negative	Percentage Paretic		
Paresis	44	38	2	4	86.3	40	—	1	90.9		
Tabes	50	39	5	16	58.0	35	—	9	70.0		
Cerebrospinal syphilis	100	34	7	59	34.0	53	—	10	53.0		
Total	194	101	14	79	52.0	128	—	20	65.9		

interest, therefore, to subject to further analysis the 117 instances (Table 3) of this type of curve. An impression diagnosis of neurosyphilis was made before puncture in forty-four, or 37 per cent, of these cases. The gold test was abnormal in twenty-seven (syphilitic zone 14, paretic zone 13) and negative in ninety instances. In an additional sixteen fluids (forty-three in all), there were present other spinal fluid abnormalities, usually a positive Wassermann test, to corroborate the mastic 3 curve. However, since this curve was the only abnormality present in seventy-three patients, its import still remains doubtful, and it should be interpreted only in the light of clinical evidence and other changes in the spinal fluid.

As a paretic type of curve has been found so much more frequently with the mastic than with the gold test in this series, its prognostic import as an indication of paresis is of less value than that of the gold test. Of the 395 positive mastic curves, 271 were of the paretic type, while of 283 positive gold curves, 199 were paretic. An impression still prevails among many physicians that a paretic gold curve always means paresis, present or likely to develop in the future. This type of colloidal curve is, however, fairly common in other neurosyphilitic diseases than paresis. In Table 4, this fact is amply illustrated. From this evidence the conclusion is permissible that the paretic type of colloidal test is so frequently present in tabes and diffuse cerebrospinal syphilis as to render it valueless as pathognomonic evidence of paretic neurosyphilis. This conclusion is supported by the fact that neurosyphilitic patients with paretic colloidal curves have been followed for years without the slightest evidence of mental damage. Obviously, therefore, the paretic mastic curve is less reliable than the gold as an indication of paresis, since it occurs with greater frequency in other types of neurosyphilis.

SUMMARY AND CONCLUSION

One thousand, seven hundred and seven spinal fluids have been studied to determine the comparative values of the colloidal mastic and colloidal gold tests. All other evidence, both clinical and serologic, was utilized in the analysis. It was found that in 1,498 fluids or 87.7 per cent, there was agreement between the two tests. There was disagreement in 209, or 12.3 per cent, and in these cases the mastic test was more often positive than the gold. Clinical evidence and other spinal fluid changes tend to support a positive mastic test in spite of a negative gold test. It is pointed out that a "mastic 3" curve is of doubtful import and must be interpreted in connection with clinical and other serologic evidence. Excluding multiple sclerosis and epidemic encephalitis, abnormal colloidal curves, either gold or mastic, are practically pathognomonic of neurosyphilis. However, a paretic type of colloidal curve, although almost constant in paresis, is not necessarily indicative of that disease, since it may occur in other neurosyphilitic diseases. A paretic mastic curve is of less diagnostic or prognostic import than a paretic gold curve.

The mastic test is recommended for adoption as an integral part of spinal fluid studies partly because the simplicity of preparation of the reagents and their stability and the ease of performance of the test render it suitable for small laboratories lacking facilities for the more elaborate colloidal gold test, and partly because its delicacy is equal to or slightly greater than that of the gold test.

BOOK REVIEWS

THE TREATMENT OF DIABETES MELLITUS By ELLIOTT P JOSLIN
Price \$8 Philadelphia Lea and Febiger, Third edition, 1923

Only seven years ago, Joslin wrote the first edition of his "Treatment of Diabetes Mellitus," a book of 440 pages, based on a study of 1,000 cases. The third edition is based on a study of 3,000 cases, and contains 784 pages. Dedicated "to Banting and Best and the Toronto group of insulin workers," it plunges at once into the midst of things diabetic with a 100 page discussion of insulin. The reading of these first pages is as interesting as romance, and highly instructive as showing the remarkable potency of the new therapeutic agent. The fast accumulating literature is digested and discussed, and here, as through the rest of the book, Joslin's faculty of adopting everything good for his diabetic patients is exhibited. Although the story of insulin is still too new to permit final conclusions, the reviewer is impressed with the careful and painstaking manner in which Joslin expresses his conclusions at the present time.

The dietary treatment of the disease is in the throes of controversy between the adherents of various methods of feeding. In this book, Joslin takes a broad stand, utilizing for his own treatment the best he can find in the observations and publications of his colleagues. He believes in the value of undernutrition to render the diabetic aglycosuric. The carbohydrate ration of the severe diabetic is what he can tolerate. Protein should be between 0.33 gm and 1 gm per kilogram of body weight. He accepts the principle that the actual quantity of food which the diabetic metabolizes is different from the actual quantity he consumes. "The caloric intake of the diabetic has been raised 31 per cent over that of the period ending in 1917."

Throughout these pages, one finds a philosophic attitude toward all that is new in the disease and a practical appreciation of all that is old and proved.

PULMONARY TUBERCULOSIS By MAURICE FISHBERG, M.D., Clinical Professor of Medicine, University and Bellevue Medical College, Chief of the Tuberculosis Service, Montefiore Hospital, New York City. Third edition, revised and enlarged. Cloth. Pp 891, illustrated with 129 engravings and 28 plates. Price \$8.50 Philadelphia Lea and Febiger, 1922.

This edition, the third, has been completely revised and enlarged. The publishers reset the entire book, thereby affording opportunity for the radical changes that have been made. Two new chapters have been introduced, one on the reciprocal relations between pulmonary tuberculosis and certain physiologic and pathologic processes, the other on the medicolegal and insurance aspects of tuberculosis.

This work has undoubtedly been the best "single volume text" in English on pulmonary tuberculosis, and the present edition only serves to make its position more tenable. It is clearly written and well arranged for easy reference, all cardinal points are italicized, due credit is given for the work of others, and accurate references to the literature are appended. There are many new illustrations in this edition, in addition to those used in former editions, and they are all printed on good paper, making them clear and useful.

There is no chapter on the subject of occupational therapy in the treatment of tuberculosis, the author practically dismissing the subject with the statement "A patient during the active course of phthisis in any stage should have no occupation at all. He cannot work, he must not attend to any vocation which requires physical or mental exertion."

This book is one of the best for use as a text for students, or for reference for the busy practitioner.

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THE MECHANISM OF PERIPHERAL STASIS IN MYOCARDIAL INSUFFICIENCY

CAPILLARY AND VENOUS PRESSURES¹

ERNST P BOAS, M D

AND

GEORGE DOONEIEF, M D

NEW YORK

The peripheral manifestations, such as hepatic and pulmonary congestion, engorgement of the veins and edema, that accompany an impaired circulation are conventionally explained by assuming that with the failing heart action there is a rise in pressure in the right auricle which impedes the venous flow to the heart, that this, in turn, causes engorgement of the veins and a heightened venous pressure which eventually is transmitted to the capillaries "The increased venous pressure spreads to the peripheral parts, acting not only so as to dilate the peripheral vessels, but also to retard the capillary flow. The increased capillary pressure results in an exema or filtration of fluid into the capillary spaces, which is responsible for the edema and ascites on the one hand, and the concentration of blood evidenced by polycythemia on the other"¹

Measurements of the venous pressure in patients with myocardial insufficiency have been adduced to support this view Clark,² using Hooker's method, and Moritz and von Tabora,³ Schott⁴ and Marks,⁵ using the direct method devised by the first of these authors, all report an elevation of venous pressure in cardiac insufficiency. Clark found that a rise in pressure may precede the clinical signs of cardiac failure,

¹ From the Medical Division, Montefiore Hospital for Chronic Diseases
1 Wiggers, C J Nelson's Loose-Leaf Living Medicine 4 259, 1920

2 Clark, A H A Study of the Diagnostic and Prognostic Significance of Venous Pressure Observations in Cardiac Disease, Arch Int Med 16 587 (Oct) 1915

3 Moritz, F, and von Tabora, D Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsch Arch f klin Med 98 475, 1910

4 Schott, E Die Erhöhung des Druckes in venosen System bei Anstrengung als Maas für die Funktionstüchtigkeit des menschlichen Herzens, Deutsch Arch f klin Med 108 537, 1912

5 Marks, H E The Clinical Determination of Venous and Capillary Pressures, Med Clin N A 4 239, 1920

and Schott that the rise in venous pressure after exercise is proportional to the degree of insufficiency of the heart.

A similar elevation of the capillary blood pressure has been noted by several authors, notably by Krauss⁶ and von Basch⁷. The method for the determination of the capillary pressure that was employed by both of these authors, however, depended on the palping of the skin when measured pressure was exerted upon it. It has been shown that this technic is quite inaccurate, and their conclusions, therefore, have little value⁸. Recently, however, Liebesny,⁹ employing a more accurate method, has reported an elevation of capillary pressure in patients with venous stasis.

Sir James Mackenzie¹⁰ has called into question the back pressure theory of heart failure and has pointed out that the primary cause of a failing circulation is weakness of the heart muscle. He says:

The objective signs of heart failure, such as dropsy and venous and hepatic engorgement, are usually spoken of as signs of back pressure, but they are probably due to an inefficiency of the driving power. The blood passes through the capillaries at a slow rate, impairs their nutrition, and allows transudation to take place, which we call dropsy. Under certain circumstances, this enfeebled circulation leads to great engorgement of the venous side of the circulation. Dilatation of the tricuspid and venous orifices may arise, so that we get regurgitant waves of blood sent back into the veins and the liver by contraction of the auricle and ventricle. Under these circumstances "back pressure" does modify the circulation and produce definite symptoms. But these results occur in only a small proportion of cases of heart failure and by the time they appear the heart failure has reached an advanced stage.

The chance observation that in several patients with myocardial insufficiency the readings of capillary blood pressure were low drew our attention to this problem. We have therefore studied a series of nineteen patients, noting the clinical signs and symptoms and measuring the venous and capillary pressures. Most of the patients were reexamined at an interval of several weeks. For the venous pressure determinations we followed the technic of Moritz and von Tabora,³ the most accurate one that has been described. Measured by this method the normal figures for venous pressure range from 1 to 10 cm of water, most frequently from 4 to 8 cm, with an average figure of 5.2 cm. With cardiac insufficiency the figures may rise to 20 or 25 cm of water. The highest reading was 32 cm. For the capillary pressure determina-

6 Krauss, H. Der Kapillardruck, Samml klin Vortrage (inn Med) **13** 315, 1914.

7 Von Basch, S. Experimentelle und klinische Untersuchungen über den Capillardruck Internat Beitr z inn Med **1** 65, 1903.

8 Danzer, C S., and Hooker, D R. Determination of the Capillary Blood Pressure in Man with the Microcapillary Tonometer, Am J Physiol **52** 136 (May) 1920.

9 Liebesny, P. Die Capillardruckmessung beim Menschen, Klin Wchnschr **2** 521, 1923, Arch f d ges Physiol **198** 215, 1923.

10 Mackenzie, J. Diseases of the Heart, Ed 3, London, 1913, p 26.

tions we employed the method described by Danzer and Hooker⁸ which we have been using in our other studies of capillary pressure. For details reference may be had to the original communication of Danzer and Hooker and to our first paper.¹¹ The normal capillary pressure as determined by this method is about 20 mm of mercury but the readings in different capillaries in the same person and in different normal persons may vary from 5 to 30 mm of mercury. Cases in which most of the readings are above 25 or below 10 are rare.

In all cases the venous pressure was first estimated and the capillary pressure was measured from thirty to sixty minutes later. The capillary pressure was measured with the patient in a sitting posture with the hand at heart level. Our observations are presented in Table I.

In Cases 1 to 5 the patients showed a heightened venous pressure accompanied by a normal capillary pressure which had a tendency to be low. They all gave clinical evidence of definite myocardial insufficiency. The patients in Cases 6 to 12 presented normal venous and capillary pressures. In them the signs of failing circulation were less evident. Cases 13 to 16 in which high venous pressures are associated with high capillary pressures are more difficult of interpretation. They are with one exception cases of hypertension which have consistently shown high capillary pressures. The capillary pressure in Case 13 of which we have records for the past two years has always been high. The patient in Case 15 was observed over a period of one year and he had consistently high capillary pressure readings even at a time when he gave no evidence of circulatory failure. The patient in Case 16 is the only one of a series of 130 whom we have observed exhibiting a normal blood pressure and a high capillary pressure yet her venous pressure barely exceeds the normal. In view of our other observations we do not believe that in this group of cases the elevation of capillary pressure is determined by the increased venous pressure. The patient in Case 17 with hypertension a low venous pressure and a high capillary pressure confirms this opinion.

It is worthy of note that in those patients in whom studies made on two occasions showed a significant variation of venous pressure there was no constant parallel alteration of the capillary pressure.

In an attempt to obtain further information of the effect on the capillary pressure of a heightened venous pressure the following experiment was performed. A young man with healthy circulatory organs was placed on his back on an examining table in such a position that simultaneous readings of venous and capillary pressures could be made. A blood pressure cuff attached to a mercury manometer was placed around the arm that was used in the examination and the hand was

¹¹ Boas E P and Frant S. The Capillary Blood Pressure in Arterial Hypertension. Arch Int Med 30:40 (July) 1922.

TABLE 1—*Observations on Author's Patients*

Case	Date	Diagnosis	Venous Pressure, Cm of Saline	Range of Capillary Pressure, Min of Mercury	Number of Capillary Readings	Blood Pressure	Myocardial Insufficiency	Comment
1	9/29/23 5/29/23	Rheumatic heart disease, mitral stenosis, aortic insufficiency, auricular fibrillation	29 3 33 1	17 - 31 4 - 18 15 - 20	19 20 4	178/ ? 220/130	Severe Severe	Dyspnea, orthopnea, cyanosis, distended veins edema Marked dyspnea, orthopnea, cyanosis, distended veins, ascites, edema of feet and back.
2	3/27/23	Myocardial degeneration, chronic nephritis, chronic bronchitis	15 5	5 - 6 10	18 3	144/ 84	Severe	Dyspnea, general cyanosis, ascites, edema
3	3/27/23 5/23/23	Rheumatic heart disease, mitral stenosis, auricular fibrillation	14 4 16 4	3 - 4 5 12 - 17	2 11 13	138/ 82 140/ 80	Moderate Moderate	Cyanosis, distended veins, slight dyspnea Condition slightly improved
4	4/10/23	Chronic bronchitis, hypertension, cardiac dilatation and hypertrophy	12 1	10 - 5 10 - 12	2 5	180/120	Severe	Orthopnea, marked cyanosis, distended veins, ascites, edema
5	4/23/23 7/10/23	Rheumatic heart disease mitral stenosis, aortic insufficiency, auricular fibrillation	11 2 11 4	5 - 8 12 6 - 10	9 8	100/ 70 132/ 88	Moderate Moderate	Cyanosis, slight dyspnea, distended veins No change
6	5/23/23	Bronchiectasis, cardiac hypertrophy and dilatation	10 1	3 10 11	6 10 12	140/ 90	Slight	Slight cyanosis and dyspnea
5/10/23			7 3	3	12-		Slight	No change
7	4/23/23	Exophthalmic goiter, auricular fibrillation	8 2	10 - 13 23 - 30	8 4	150/ 76 148/ 70	Slight Slight	Asthenia, slight dyspnea No change
8	4/ 9/23 5/ 9/23	General arteriosclerosis, hypertension	7 9 5 2	5 17 15	8 1 10	184/ 90 170/ 90	Slight Slight	Slight cyanosis, slight distension of veins General condition improved

6	1/13/23	Syphilitic aortitis, aortic insufficiency, cardiac hypertrophy	57	10	4	120/ 42	Slight	Slight cyanosis
	5/ 7/23	Rheumatic heart disease, mitral stenosis, aortic insufficiency	78	3 - 4	11	118/ 32	Slight	Condition unchanged
10	4/13/23	Bronchiectasis, chronic bronchitis, cardiac hypertrophy and dilatation	58	5 - 8	10	150/ 50	Severe	Marked cyanosis and dyspnea, distended veins, edema
	5/ 7/23	Chronic bronchitis, emphysema, cardiac hypertrophy and dilatation	39	9 - 10	14	130/ 44	Severe	No change in condition
11	3/30/23	Hypertension, myocardial degeneration, auricular fibrillation, bronchiectasis	49	7 - 15	16	140/ 85	Moderate	Dusky cyanosis, dyspnea, distended veins
	5/ 9/23	Myocardial degeneration, general arteriosclerosis, chronic nephritis	26	3 - 5	8	126/ 76	Moderate	Slight edema
12	4/13/23	General arteriosclerosis, chronic nephritis, hypertension, and dilatation	31	26 - 28	8	172/ 98	Moderate	Cyanosis, dyspnea
	5/ 7/23		36	10 - 16	4	158/ 98	Moderate	No change
13	3/29/23		19 4	40 - 47	37	220/110	Severe	Dyspnea, cyanosis, distended veins, edema
	5/23/23		17 4	12 - 18	20		Severe	Slight increase in edema
14	3/30/23		14 4	20 - 45	28	140/ 95	Severe	Dyspnea, cyanosis, distended veins, edema, pulsus alternans
	7/ 9/23		9 7	8 - 9	5		Severe	Grillop rhythm, edema
15	3/29/23	General arteriosclerosis, chronic nephritis, hypertension, cardiac hypertrophy and dilatation	10 7	40 - 80	9	200/140	Severe	Puffiness of face, dyspnea, edema
	5/ 2/23	Chronic nephritis	9 9	40 - 60	12	120/ 80	Slight	Nephritic facies, slight edema
	5/23/23	Hypertension, cardiac hypertrophy and dilatation	11 7	25 - 33	7		Slight	No change
17	4/ 5/23	Chronic bronchitis and emphysema, cardiac hypertrophy and dilatation	6 0	45 - 55	6	220/120	Slight	Slight cyanosis and dyspnea
	5/10/23		1 5	32 - 36	6	212/136	Slight	No change
18	4/13/23	Rheumatic heart disease, mitral stenosis, aortic insufficiency, auricular fibrillation	9 8	13 - 15	6	120/ 78	Moderate	Marked cyanosis, dyspnea, distended veins
	5/ 9/23		8 8	11 - 13	5	140/ 78	Slight	No change
19	3/22/23		9 1	21 - 31	16	148/ 80	Severe	Dyspnea and cyanosis
	5/ 9/23		14 9	15 - 28	15	150/ ?	Severe	Venous pleural effusion, edema, General condition about the same

placed at heart level. The venous pressure manometer was filled with 2 per cent sodium citrate solution to prevent clotting of blood in the needle which was left in the vein over a considerable period of time. Control readings were made until both venous and capillary pressures were stabilized. Then the blood pressure cuff was inflated with air up to a certain point and maintained at that pressure while repeated readings of the venous and capillary pressures were made. The same group of capillaries were always used for the pressure estimations. The experiment was performed on three different days with similar results. Table 2 gives a protocol of the last session.

TABLE 2.—*Pressure Estimations*

Time	Pressure in Sphygmomanometer Cuff, Mm of Mercury	Venous Pressure, Cm of Citrate	Capillary Pressure, Mm of Mercury
2 30 to 2 40	0 0 0 0	5 1 3 2 5 0 7 8	17 16—6 readings 17 10
2 41	20		
2 42	20	18 5	13—3 readings
2 44	20	20 2	14—6 readings
2 45	20	20 3	13—3 readings
2 46	0		
2 47	0	7 8	15—5 readings
2 47½	30		
2 49	30	30 5	10—3 readings
2 50	30	33 1	13—2 readings
2 51	30	34 2	8—6 readings
2 52	0		
2 56	0	8 1	14—4 readings
2 59	v	7 8	23—3 readings
3 00	0	7 5	15—5 readings
3 00½	40		
3 02	40	21 8	16—2 readings
3 03	40	32 1	10—4 readings
3 04	40	37 8	15—3 readings
3 05	40	39 0	10—2 readings

The data presented in the two tables show that within the limits of the pressures that were studied the venous and capillary pressures are independent. A venous pressure ranging as high as 39 cm of water may be accompanied by a low capillary pressure, and a low venous pressure may be associated with a high capillary pressure. In the experiment in which the venous pressure was artificially increased it was noted that while the blood pressure cuff was inflated, the color of the skin in the microscopic field assumed a dusky red color, but there was no engorgement of the visible capillaries.

These results are of considerable theoretic interest. They afford additional evidence of the functional independence of the capillaries. Since the venous pressure with a failing circulation rarely exceeds the figures noted in our observations, they give additional support to the

view that peripheral stasis is not conditioned by back pressure effects but rather by a lessened propelling force of the left ventricle. This diminished motive power of the heart results in a slowing of the blood stream, particularly in the peripheral vessels. A greater oxygen unsaturation of the capillary blood ensues, which is followed by a dilatation of the capillaries. Whether the dilatation is determined by the want of oxygen, by the absence of some hormone, as suggested by some of the work of Krogh, or by impaired nutrition of the capillary wall resulting from an inadequate blood flow, is unknown. Undoubtedly the dilated capillary walls are more permeable and at a certain stage of the process filtration edema will occur.

A number of physiologic observations seem to throw doubt on the correctness of our observations. The reports by earlier investigators can be ignored because their methods for the determination of capillary pressures were inaccurate. However, Danzer and Hooker⁸ have noted an increase of from 2 to 3 mm of mercury in the capillary pressure, induced by the Valsalva experiment, and an elevation of 2.5 mm of mercury when a rubber band was loosely wound around the finger. We believe these changes of pressure are so small that they fall within the limits of error of the method employed.

More difficult to correlate with our findings are the observations of several authors that the blood pressure in any group of capillaries depends on their position in relation to the level of the heart. This is attributed to the hydrostatic pressure of the column of blood.¹² Thus Krogh reports that when the hand is lowered 29 cm the capillary pressure rises 26.2 cm of blood, which is equivalent to 20.2 mm of mercury. Von Kries found that lowering the hand 28.5 cm raised the capillary pressure by 11 cm of blood or 8.1 mm of mercury. Kylin, on the other hand, reports that lowering the hand 43 cm raises the capillary pressure only 3.8 cm of blood or 3 mm of mercury. We have repeated these measurements and have found on one occasion that lowering the hand 37.5 cm raised the capillary pressure 18.1 cm of blood, or 14 mm of mercury, on another, that a lowering of 41 cm raised the capillary pressure 12.6 cm of blood or 9.7 mm of mercury.

Our findings lend themselves to several interpretations. First, that a venous pressure as high as 39 cm of water may have no effect on the capillary pressure. Again, it may be that the failing driving power of the heart, on the one hand, and a reflex vasoconstriction from the inflation of the sphygmomanometer cuff, on the other, lower the capillary pressure enough so that the slight increase caused by the elevated venous pressure is not evident. For example, a patient may have a

12 Tigerstedt, R. Die Physiologie des Kreislaufes, Berlin, 3 274, 1922
Krogh, A. The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922, p 220

capillary pressure of 20 mm of mercury. With the failing propelling force of the heart, the capillary pressure may drop to 5 mm of mercury. The heightened venous pressure may raise the capillary pressure by 5 mm, giving a resultant capillary pressure of 10 mm, which is lower than it was before myocardial insufficiency set in.

Either of these interpretations lead to the conclusion that the chief cause for peripheral stasis and edema lies in the weakened cardiac contraction and not in back pressure effects.

The only other explanation that suggests itself is that we have measured by the Danzer and Hookei method not the true capillary pressure but the pressure in the precapillary arterioles. The low capillary pressures found by Carrier and Rehberg¹³ would point in this direction. On the other hand, the fact that we observed the effect of hydrostatic pressure on the readings makes us believe that we are dealing with real capillary pressures.

Whatever may be the final decision, the results obtained in this study give added significance to the high capillary pressures reported by one of us in certain cases of hypertension¹⁰ and demonstrate conclusively that these high readings were not determined by a high venous pressure.

¹³ Carrier, E. B., and Rehberg, P. B. Capillary and Venous Pressures in Man, *Skand Arch f Physiol* **44** 20, 1923.

A STUDY OF THE MECHANISM OF ABSORPTION OF SUBSTANCES FROM THE NASOPHARYNX

HERRMANN L BLUMGART, MD
BOSTON

Two previous communications have indicated that the nasopharynx constitutes an area of peculiar physiologic significance. Observations on several cases of diabetes insipidus¹ uniformly showed that although the watery extract of the pituitary gland was not absorbed from any other internal or external surface of the body, it nevertheless gained rapid and effective entrance through the nasopharynx. The disclosure of such an interesting physiologic mechanism raised the query whether this absorptive power might extend also to particulate matter. Using the proper precautions to prevent absorption by any other route, it was found that particulate matter in the form of pulverized lead carbonate was readily absorbed from the upper air passage of cats and dogs.² The absorption was rapid and greatly in excess of the minimal toxic dose. Although these facts demonstrated that both solutions and particulate matter might eventually traverse the normal nasopharyngeal mucous membrane with readiness, they gave no clue to the underlying mechanism.

Search of the literature revealed scattered observations which, while not bearing directly on the point, are nevertheless suggestive in this connection. Since they have been uncovered in widely dissimilar investigative fields for the most diverse purposes, it would seem worth while to gather them together in this place in an effort to gain some insight into their possible relationship, and perhaps finally to gain some clue to the function of this important area.

PHENOMENA INDICATING ABSORPTION OF SUBSTANCES THROUGH THE NASOPHARYNX

Certain observations relating to the absorption of substances in the upper air passages are of considerable interest. Klebs³ relates that it was an ancient custom among the Chinese and Hindus to vaccinate against smallpox by blowing the finely powdered virus into the nostrils. Similarly, Zerjgowsky⁴ produced active immunity in animals by administering diphtheria toxin intranasally by sprays and cotton plugs.

1 Blumgart, H L. Antidiuretic Effect of Pituitary Extract Applied Intranasally in a Case of Diabetes Insipidus, Arch Int Med **29** 508 (April) 1922

2 Blumgart, H L. Lead Studies VI, J Indust Hyg **5** 153 (Sept) 1923

3 Klebs Bull Johns Hopkins Hosp **24** 69, 1913

4 Zerjgowsky Ztschr f Immunitätsforsch, Abst **3** 602, 1910

Blumenau⁵ repeated these observations on large numbers of children, using intranasal plugs heavily soaked with undiluted toxin. Like Zerjgowsky, he found that the procedure caused no subjective symptoms, but was followed by the appearance of a small amount of anti-toxin in the blood. These experiments derive additional significance from the fact that Anderson⁶ tried in vain to immunize guinea-pigs to diphtheria by subcutaneous injections of toxin.

More exact demonstration of absorption of substances by the nasopharynx is afforded by the experiments of Sewall⁷ on guinea-pigs. He found that if 3 minimis (0.18 cc.) of horse serum were instilled intranasally into guinea-pigs, subsequent intravenous injections revealed that the animals had become either sensitized or immune. In the former group, the first intravenous injection caused speedy anaphylactic death. In the other group of animals, the first intravenous injection produced practically no reaction, and a second injection after an interval of three weeks was likewise withheld. Later work demonstrated that the transfer of immune serum conferred immunity on normal guinea-pigs, enabling the latter to withstand intravenous injections of horse serum which always proved fatal to controls. As the authors of these experiments realized, however, there was no assurance as to the site of absorption of the horse serum, since some may have reached the trachea and some was certainly swallowed.

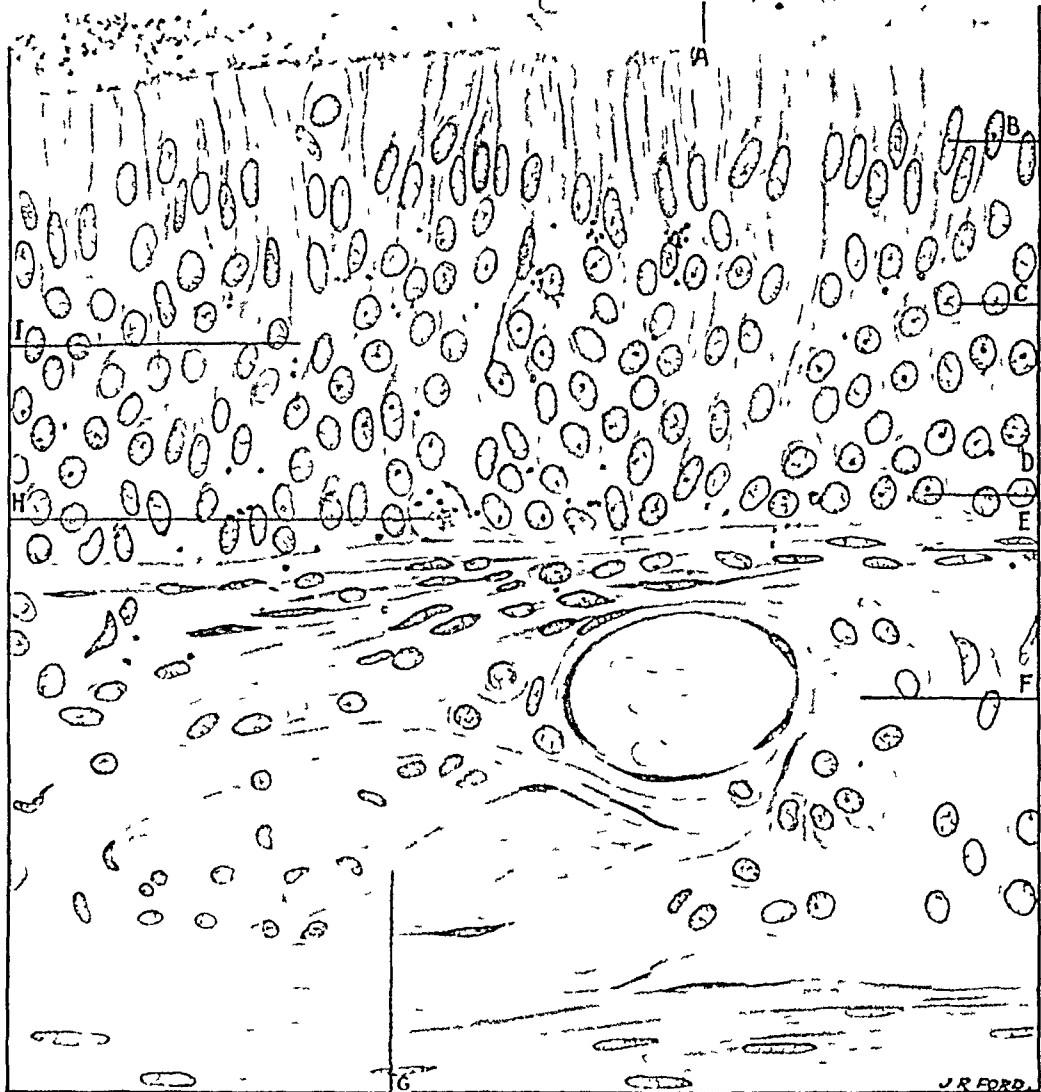
The only proof of absorption of substances actually in the nasopharynx is afforded by pituitary extract and lead carbonate. I demonstrated, in patients suffering from diabetes insipidus, that pituitary extract introduced intranasally effected a reduction in the fluid intake and urinary output entirely comparable in magnitude to hypodermic injections.¹

To determine whether particulate matter might likewise be absorbed, cats and dogs were subjected to the following experiments. The esophagus was completely occluded by two or more ligatures, the trachea opened below the thyroid, and a tightly fitting glass cannula inserted. The lumen of the free upper end of the trachea was then occluded by two or more ligatures. Definite amounts of finely powdered white lead dust were then sprayed intranasally. After from eighteen to thirty-six hours, careful necropsies were made of the animals, the entire skin, and the head, trachea and esophagus above the ligatures discarded, and the skeleton and other tissues analyzed separately for lead. The average amount of lead recovered, expressed in terms of metallic lead, was approximately 22 mg per animal. Although

5 Blumenau Jahrb f Kinderh 74 141, 1911

6 Anderson, J F Hyg Lab Bull 30, Washington, D C, p 906

7 Sewall Some Relations of the Brain and of the Olfactory Apparatus to the Process of Immunity, Arch Int Med 13 856 (June) 1914



Camera lucida drawing of section of olfactory mucous membrane

A indicates the cilia B zone of oval nuclei (sustentacular cells), C zone of round nuclei (olfactory cells) D basal cells E tunica propria, F, olfactory gland G cross section of nerve H small lymphatic, I, duct of olfactory gland

the average weight of the animals was approximately one-fifteenth that of a 60 kg man, the amount absorbed by each animal was more than twenty-two times the minimal toxic dose for a human being.

ENTRANCE OF PATHOGENIC ORGANISMS BY WAY OF THE
NASOPHARYNGEAL MUCOUS MEMBRANE

The anatomic proximity of the nasopharynx to the cranial cavity and the appearance of signs of local meningeal irritation before the manifestation of generalized invasion have naturally stimulated workers to establish an etiologic relationship. Perhaps the most incisive experimental investigations relating to the nasopharynx have been undertaken in connection with anterior poliomyelitis and cerebrospinal meningitis. Strumpell⁸ first advanced the hypothesis that the virus of poliomyelitis may reach the central nervous system by traveling along the olfactory nerves, an hypothesis which was established as fact by the researches of Flexner⁹ and his co-workers. They found "that the virus passes with readiness and constancy from the intact or practically intact mucous membrane of the nose to the central nervous system and that this membrane, next to direct intracerebral introduction of the virus, gives the readiest method of successful inoculation." Flexner and Clark¹⁰ showed that forty-eight hours after intranasal inoculation the virus could be demonstrated in the olfactory lobes of a monkey, whereas none could be demonstrated in the medulla or spinal cord. Additional evidence of the predilection of the virus of poliomyelitis to pass directly from the nasopharynx to the tissues of the central nervous system without previous hemic invasion was afforded by Clark, Fraser and Amoss¹¹. They found that 10 cc of active poliomyelitis virus could be given to a monkey intravenously without causing the disease, whereas 0.2 cc or less of the virus, when injected intracerebrally, precipitated the characteristic train of symptoms. Furthermore, when the blood serum of the animals that received the intravenous injections was injected intracerebrally, the typical train of symptoms ensued.

The importance of the nasopharynx has likewise been emphasized by the study of cerebrospinal meningitis. Extensive clinical investigations have confirmed Flexner's¹² experimental observations that the meningococcus both enters and leaves the body by way of the mucous membrane of the upper part of the nasopharynx and the posterior nares. Opinion is divided, however, on the question whether the

⁸ Strumpell Deutsch Arch f klin Med 1891, p 47

⁹ Flexner, S The Mode of Infection in Epidemic Poliomyelitis, J A M A **59** 1371 (Oct 12) 1912

¹⁰ Flexner and Clark Proc Soc Exper Biol & Med **10** 1, 1912-1913

¹¹ Clark, Fraser and Amoss J Exper Med **19** 223, 1917

¹² Flexner, S Epidemic Meningitis, J A M A **69** 639 (Aug 25) 1917

organism passes directly to the central nervous tissues by way of the lymph spaces about the olfactory nerves, or indirectly by way of the blood. Early positive blood cultures, and the occurrence of metastatic meningococcal inflammation in the joints and the heart indicate that, at least in certain cases, the latter possibility prevails.

THE ANATOMIC RELATIONSHIP OF THE NASOPHARYNX

Schwalbe,¹³ and later, Key and Retzius,¹⁴ demonstrated by skilful postmortem injections the lymphatic connection between the subarachnoid space and the lymphatics of the nasal mucosa. As they utilized rather high injection pressures in dead and consequently less resistant tissues, there was no assurance that the path they demonstrated actually obtained during life. Weed's¹⁵ admirable work, however, yielded more reliable data. He utilized subarachnoid injections of potassium ferrocyanid with postmortem fixation and precipitation by formaldehyd and hydrochloric acid. The pressures used "were slightly above normal and over considerable periods of time." Under these conditions, he found the granules of Prussian blue in the arachnoid cul-de-sacs above the cribriform plate, in the perineural spaces along the olfactory nerves as far as the nasal mucous membrane, where they lay beneath the surface in the meshes of loose connective tissue. He believed that these histologic findings indicated an accessory path of drainage for the cerebrospinal fluid and that from the loose tissue spaces it passed into the lymphatic vessels of the nasopharynx.

Although these studies show that a pathway exists between the subarachnoid space and the lymphatic spaces beneath the nasal mucous membrane, they shed no light on the mechanism or path by which substances may enter the body by traversing the mucous membrane of the nasopharynx. In view of the importance of this route in the conditions cited above, and in view of the susceptibility of this problem to experimental attack, the following work was undertaken.

OBSERVATIONS

1 *The Absorption of Fluids*—A. Crystalloids. In deciding what solution would yield the most trustworthy results, it seemed essential that the substance must satisfy certain experimental conditions.

1 The solution must be nontoxic. If the substance to be used were to traumatize the mucous membrane, there would be no assurance

13 Schwalbe Centralbl f med Wissenschaft 7 465, 1869

14 Key and Retzius Anatomie des Nervensystems u d Bindegewebes, Stockholm, 1876

15 Weed J Med Res 31 21 (Sept) 1914

that the path traversed would be the path traversed under physiologic circumstances. The circulatory alteration that such traumatization would evoke, as well as the presence of agonal and necrotic cells would inevitably distort the final picture.

2. The solution must not act as a tissue stain. Obviously if the tissues tended to absorb this solution as a selective tissue stain the presence of the substance intracellularly might merely represent a chemical combination rather than the course of a similar solution during life as it passed through the tissues of the mucous membrane.

3. The solution must be identified with certainty and be unaffected by the ordinary reagents used in preparing histologic sections.

The use of equal parts of potassium ferrocyanid and iron ammonium citrate as satisfying these conditions was suggested by the work of Weed on the cerebrospinal circulation. In none of his extensive series of researches did he find that injections of the substance acted as a tissue stain notwithstanding the fact that the solution was injected into the subarachnoid space. "The precipitated granules were uniformly found clinging to the superficial portions of the cells and not within the cell bodies." Only in certain locations such as in the arachnoid villi, did he find the granules intracellularly, and in this instance there was excellent reason to believe that it represented the true course of the fluid through a living semipermeable membrane. In all of Weed's experiments, the 2 per cent solutions were injected directly into the spinal canal for periods of many hours duration without any phenomena indicating toxicity being observed. This is the more significant on account of the enormous accentuation of toxicity drugs manifest on intraspinal injection as compared to subcutaneous or even intravenous injections.

In the experiments described in this paper, it was found that such weak solutions underwent dilution in the nasopharyngeal mucus and were not as satisfactory as stronger concentrations of 15 or 20 per cent. Cats were the animals used. The solution was sprayed by means of an ordinary atomizer, care being taken to reach all possible portions of the anterior and posterior nares. The spraying was repeated at fifteen minutes intervals and the animals sacrificed after from one to six sprayings. The animals were killed with coal gas a method which has been found to be speedy and painless and to involve a minimum of circulatory alteration.

As soon as respiration ceased the animals were rapidly decapitated, the skin removed, the skull trephined in several places in order to facilitate fixation and the tissues fixed in 10 per cent solution of formaldehyde and 5 per cent concentrated hydrochloric acid. The course of a

typical experiment, characteristic of others in this series, can be best illustrated by the following protocol

Cat Young adult Solution of potassium ferrocyanid and iron ammonium citrate equal parts used Strength of solution 20 per cent Ten cubic centimeters sprayed intranasally using ordinary atomizer distributed at fifteen minute intervals over a period of two hours, i e, 10 00 a m, 10 15 a m, 10 30 a m, 10 45 a m, 11 00 a m, 11 15 a m, 11 30 a m, 11 45 a m and 12 00 At 12 15 animal placed in gas chamber and gas turned on At 12 17 the cat was dead The animal was immediately decapitated at the level of the fifth cervical vertebra, the skin removed and discarded, the head trephined, and the head and neck structures plunged into solution of formaldehyd 10 per cent concentrated hydrochloric acid 5 per cent at 12 21 Solution changed daily On the third day dissection showed macroscopic blue coloration of the retropharyngeal lymph chain Sections of the anterior nares, of the olfactory regions, tongue and oropharynx were dehydrated in graded alcohol, embedded in paraffin, counter-stained with safranin and also with hematoxylin and van Gieson's stain The sections were then mounted

Microscopic examination of the sections of the tongue, anterior nares, and oropharynx showed a superficial deposit of the characteristic blue granular precipitate, but no evidence of any intracellular or intercellular penetration The sections of the olfactory region presented a distinctly different picture as olfactory nerve cells showed distinct blue granules in their cytoplasm and along the periphery The olfactory cells were bipolar, spindle shaped and contained round nuclei These nuclei lay deep in the mucous membrane in contrast to the small, pyramidal, basal cells which formed the deepest nuclear zone, and the sustentacular cells which formed the more superficial nuclear zone The peripheral processes of the olfactory cells were short and penetrated to the surface where they ended in a projecting tuft of hairline cilia The basal cells and the sustentacular epithelial cells failed to show any blue granular content There were characteristic granules in the loose connective tissue meshwork of the tunica propria, as well as in the lumens of some of the thin walled lymphatic vessels Particular search of the nerves failed to reveal any evidence of absorption along such routes

Control Experiment—The animal was placed in the gas chamber at 2 50 p m It was dead at 2 55 p m It was decapitated The nasopharynx was then sprayed with 5 c c of solution as above The head was plunged into 10 per cent solution of formaldehyd and 5 per cent hydrochloric acid at 3 02 The tissues were prepared and examined as above In all sections, deposition superficially of granular precipitate could be seen but no evidence of intercellular or intracellular absorption or staining

Colloids In order to ascertain whether colloids were absorbed by the same mechanism, a 5 per cent solution of colloidal silver was sprayed intranasally at fifteen minute intervals for two hours The tissues were prepared and examined in the usual way No macroscopic evidence of absorption was visible Microscopically, the tissues of the olfactory region again were the sole ones that showed evidences of penetration, the distribution being similar to that noted with potassium ferrocyanid although the concentration seemed in general somewhat less

2 *Particulate Matter*, —(a) Ivory Black To determine whether particulate matter traverses the nasal mucosa, experiments similar to the foregoing were performed, ivory black being insufflated in the dry powdered state The substance consisted of particles of varying size, that is, from particles at the lower limits of vision to those about one quarter the size of an ordinary human red blood corpuscle

After eight insufflations of this inert substance at fifteen minute intervals, the animal was killed as in the preceding experiments and the tissues examined

Macroscopically, there were no significant findings. Microscopically, an occasional minute granule was to be seen on the periphery of an olfactory nerve cell or in the loose mesh work of the tunica propria.

(b) *Fixed Staphylococcus aureus* To ascertain whether larger particles such as fixed organisms are absorbed through the nasal mucous membrane, cultures of *Staphylococcus aureus* were taken, washed and fixed in solution of formaldehyde. The organisms were then stained for four days in the cold with Ehrlich's acid hematoxylin. The suspension was then washed repeatedly in successive washings of distilled water until the supernatant fluid showed no sign of coloration. One cat was given eight insufflations of the suspension of organisms and then killed, another after similar treatment was killed after twenty-four hours. None of the tissues examined gave macroscopic or microscopic evidence of absorption of the organisms.

In order to obtain some index of the relative ease with which crystalloids and colloids are absorbed the following experiment was undertaken.

Cats were anesthetized with urethane subcutaneously. The trachea was identified and severed, the upper end occluded and the lower end attached to a tracheal cannula. The esophagus was also identified and ligatured. A tightly fitting postnasal plug was introduced into the postnasal space in order to isolate the nasopharyngeal cavity. A cannula was introduced into the bladder so as to include within its lips the orifices of both ureters. A standard solution of phenolsulphonephthalein was then prepared of such strength that 1 cc contained 6 mg. At 12:02 1 cc was sprayed intranasally. At 12:12 the urine issuing from the cannula became definitely pink, as it was caught in a test tube containing sodium hydroxid. At 1:42 1 cc of the standard solution was given intravenously. The first marked change in the color of the urine was noted at 1:47.

One cc of a 5 per cent solution of potassium iodid was similarly introduced but no positive test was secured until one and a half hours had elapsed. The test used was the sodium nitrate and sulphuric acid test which was found sensitive to 1 minim (0.05 cc) or a 1:4000 solution of potassium iodid that is approximately 0.00002 gm.

In animals similarly prepared 1 cc of phenolsulphonephthalein given orally appeared in a quantity to give color reaction only after from one-half to one hour.

COMMENT

The granules of potassium ferrocyanide the molecules of colloidal silver and the small particles of ivory black found in the tissues may safely be assumed to represent the true physiologic course of solutions as they traverse the mucous membrane of the nasal cavity. In the case of the potassium ferrocyanide precipitate the control experiments eliminate the possibility of the potassium ferrocyanide-iron ammonium citrate solution having entered the cell by virtue of its chemical properties. Were the phenomena witnessed an expression of such staining one would expect it to be diffuse and relatively uniform. These observations are in accord with the more extensive experience of Weed¹⁵ as recorded in his researches on the cerebrospinal circulation.

These experiments therefore indicate that solutions both crystalloid and colloid may pass by way of the olfactory receptor nerve cells into the lymphatic meshwork beneath the nasal mucous membrane and thence

to the retropharyngeal lymph nodes. A similar path seems to be traversed successfully by occasional minute particles of an inert substance such as ivory black. The path along the peripheral portions of the cell may well be analogous to the distinct spaces that Mott¹⁶ has demonstrated about the capillaries and about each nerve cell in the brains of animals with experimental anemia. In view of the difficulty with which inert particles have been found to traverse the nasal mucous membrane, the relatively large amount of lead found deposited in the tissues of animals in previous experiments must receive one of two explanations. Either the lead carbonate was first dissolved in the mucus and then absorbed as a true solution, or the toxic action of the lead rendered the mucous membrane more permeable to the passage of particles of lead carbonate. It is, of course, entirely possible that both factors tended to operate.

It should be noted that the absorption of substances is accomplished only by those cells which conform to the description of the olfactory nerve cells. The observation of such absorption only in that area which conforms to the anatomic distribution of the olfactory nerve cells is confirmatory evidence. In view of this fact, the unique ability of the nasopharynx to absorb such substances as pituitary extract becomes correlated with the equally singular anatomic structure of the nasal olfactory mucous membrane. As Schaeffer¹⁷ remarks:

The cells that retain the olfactory characteristics and functions are known as neuroblasts. They remain in the walls of the nasal pits, become bipolar olfactory cells and by central processes become connected with the brain. They represent morphologically the ganglionic cells in the dorsal (sensory) roots of the spinal nerves, and retain the primitive location of such sensory cells in the surface epithelium. The olfactory cells are unique in this regard among neuro-epithelial elements.

The failure of previously fixed organisms to be absorbed in the foregoing experiments is not surprising, for under the conditions they represent merely inert particles of relatively large dimensions. No analogy can be drawn between the fate of such inert particles and living organisms. The question as to whether the virus of poliomyelitis and the meningococcus utilize the same pathway as the true solutions in these experiments, is of considerable interest. All clinical and experimental observations evidently agree that the precise site of election of both organisms is over the olfactory mucous membrane, exactly that area through which substances have been shown to pass in these experiments. Even if one assumes the course of infection in these diseases to be that detailed above, the exact pathway from the lymphatics of

16 Mott Lancet, Pt 2, 1 and 79 (July 2 and 9) 1910

17 Schaeffer The Nose, Paranasal Sinuses, Nasolacrimal Passages, and Olfactory Organs, in Man, Philadelphia, P Blakiston's Son & Co, 1920, p 267

the tunica propria to the tissues of the central nervous system is not yet absolutely clear. According to the researches of Weed, the normal path of cerebrospinal fluid drainage is from the subarachnoid space along the perineurial spaces of the olfactory nerves outward into the loose meshwork of lymphatic spaces of the submucosa. The absence of granules in the perineurial spaces in the experiments presented after intranasal spraying of potassium ferricyanide are in accord with Weed's experiments, for, were the direction of flow from the periphery toward the subarachnoid space, one would have expected to find granules along this route. It must be remembered, however, that in these locations we are dealing with extremely small differences of pressures such as would readily permit reversals of current. That such reversals may actually occur is suggested by certain experimental considerations. Weed¹⁸ found that if lumbar puncture was performed on monkeys soon after the intravenous injection of a dose of *Bacillus mucosus-capsulatus* fatal meningitis ensued, whereas in a series of controls in which lumbar puncture was not performed double the intravenous dose was not attended by any such consequence. The ascending course of tetanus toxin along the nerves is also exceedingly suggestive in this connection especially since it has been demonstrated that the perineurial spaces of such nerves likewise constitute an accessory path of cerebrospinal fluid drainage. The admirable studies of Friedenwald¹⁹ in the virus of herpes simplex also bear on this point. He found that after a rabbit had received a corneal inoculation of herpes simplex the virus could be transmitted from rabbit to rabbit with the production of typical lesions by removing the gasserian ganglion, emulsifying it in saline and inoculating it into the cornea. Every such gasserian ganglion examined microscopically showed definite lesions not found in the normal controls. Similarly, Flexner and Lewis²⁰ have shown that the virus of poliomyelitis will travel up the sheath of the sciatic nerve affecting first that side of the cord on which the injection was made. The final evidence that such reversals of current do occur is afforded by Weed's recent experiments, in which he studied the paths of drainage after intravenous injections of hypertonic solutions.

It would seem that any such striking property as has been shown to exist in the olfactory cells might well be related to their chief function. In connection with the ability of these cells to transmit solutions, it is

18 Weed. Production of Meningitis by Release of Cerebrospinal Fluid. J. A. M. A. 72: 190 (Jan. 18) 1919.

19 Friedenwald. Arch. Ophth. 53: 105 (Feb.) 1923.

20 Flexner, S., and Lewis, P. A. The Transmission of Epidemic Poliomyelitis to Monkeys. J. A. M. A. 53: 1913 (Dec. 4) 1909.

21 Weed. Am. J. Anat. 31: 3 (Jan.) 1923.

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¹⁸ Weed Production of Meningitis by Release of Cerebrospinal Fluid, J A M A **72** 190 (Jan 18) 1919

¹⁹ Friedenwald Arch Ophth **53** 105 (Feb) 1923

²⁰ Flexner, S., and Lewis, P. A. The Transmission of Epidemic Poliomyelitis to Monkeys, J A M A **53** 1913 (Dec 4) 1909

²¹ Weed Am J Anat **31** 3 (Jan) 1923

interesting to quote Parker²² to the effect that "the adequate olfactory stimulus for both water inhabiting and air inhabiting vertebrates is a solution in contact with the olfactory hairs and perhaps formed in part within these bodies" (p 81). That such solutions are in an eminently favorable situation to act chemically on the olfactory receptors is indicated by these experiments.

The presence of an area of such unique absorptive power naturally excites curiosity as to whether it may play some other rôle in addition to its possible importance in olfaction. The work of Sewall, previously cited, strongly suggests that nasopharyngeal absorption may play an important rôle in establishing resistance to the "droplet infections." The anatomic design of the upper respiratory passages which serve to prevent the progress of particles to the more vulnerable pulmonary passages, the power of mucus to dissolve organisms and the ability of the nasopharynx to absorb such decomposition products and transmit them to the underlying lymphatics constitute a chain of forces splendidly adapted to the creation of natural active immunity.

SUMMARY AND CONCLUSIONS

1 Previous observations, clinical and experimental, demonstrated that the nasopharynx constitutes an area of singular absorption.

2 The experiments here presented indicate that crystalloids, colloids and, to a lesser extent, particulate matter, traverse the nasopharyngeal mucous membrane by being absorbed by way of the olfactory nerve cells and thence to the systemic lymphatics.

3 The clinical and physiologic significance of these findings is discussed.

22 Parker Smell, Taste and Allied Senses in Vertebrates, Philadelphia, J B Lippincott Co, 1922

OBSERVATIONS ON A GROUP OF MARATHON RUNNERS

WITH SPECIAL REFERENCE TO THE CIRCULATION *

BURGESS GORDON, M D , S A LEVINE, M D
AND
A WILMAERS, M D
BOSTON

PART 1 THE VITAL CAPACITY OF THE LUNGS BEFORE AND AFTER A MARATHON RACE

The American marathon race takes place annually in Boston on April 19. Generally, the men who participate in this 25 mile race are the best long distance runners in the United States and Canada. It, therefore, seemed to be an exceptional opportunity to observe the effect of prolonged vigorous training and a strenuous prolonged effort on certain features of the circulation. The first part of the paper deals with observations on the vital capacity of the lungs, the second with the size of the heart as determined by roentgenograms and the third with some miscellaneous notes, such as the blood pressure and general condition of the runners.

Most observers who have studied the vital capacity of the lungs in health and disease have noted that some of those better trained attained abnormally high figures. With this in mind, determinations of all the participants in the American marathon race were made just before the race. These men had all been training for some months immediately preceding the race, and most of them had been doing long distance running for from five to fifteen or more years. It is fair to say that such a group of men should show the effect of prolonged vigorous training, as running ten or more miles repeatedly and frequently under the pressure of competition year in and year out should test or develop the circulatory mechanism to a maximum.

One must immediately ask which method should be used in determining the percentage of the normal vital capacity. Are the figures to be calculated on a height basis or by the surface area method? Peabody,¹ in his early work, originally made three groups, depending on the height, but soon it was appreciated that important errors resulted when the shorter and taller members of each group were compared to the same standard. Obviously, it would have been more satisfactory if average normal figures had been available for each centimeter of

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston

¹ Peabody, F W, and Wentworth, J A Clinical Studies on Respiration, Arch Int Med 20 433, 443 and 468 (Sept) 1917

height. The small number of observations of Peabody's series did not permit this. Subsequently, West² made calculations using the surface area as his basis, and he thought that for males, the normal vital capacity in liters should be 2.5 times the surface area in square meters. This assumes that the vital capacity of the lungs is a function of the surface area. This, it seems, is not necessarily true from either a theoretical or practical standpoint. However, for persons of normal weight, it probably would work out satisfactorily. More recently, Hewlett and Jackson³ made charts of a large series of young adult males and concluded that the vital capacity was a simple function of the height, that is the vital capacity in cubic centimeters was 50 and the height in centimeters, 4,400. This means that the taller the person, the greater will be the vital capacity, and the graph when plotted will be a straight line and each increment in height will have the same increase in vital capacity.

In Table 1 are charted all the readings made in this study. The actual vital capacities obtained before the race are noted, then the calculated normal figure follows determined from the surface area, and then the percentage of normal. For purposes of comparison, a further calculation is made on the basis of height. There are apparent wide variations in the different runners. On the basis of surface area, the lowest figure is 71 per cent and the highest 138 per cent, and on the basis of height the lowest is 76 per cent and the highest 138 per cent. The average of the two methods is 98.6 per cent using the surface area and 103.3 per cent using the height standard. This indicates that even the most extreme kind of training probably has little influence, if any, on the vital capacity of the lungs, for certainly the general average of so large a group would have reflected the results of training by a figure approximately from 15 to 20 per cent above the normal. There were nine men with figures more than 15 per cent below normal, using the surface area method, and four using the height method. There were only three more than 15 per cent above normal with the former method and ten with the latter. One is struck by the fact that the vital capacities varied a great deal from below normal to above normal and that there was no important relation between the vital capacity of the lungs and the order in which the runners finished.

Observations were made on twenty of the runners a few minutes after they finished the race. They were quite exhausted and fatigued, although they made a strenuous effort in blowing. The vital capacity

² West, H F. Clinical Studies on Respiration, Comparison of Various Standards for Normal Vital Capacity of Lungs, *Arch Int Med* **25** 306 (March) 1920

³ Hewlett, A W, and Jackson, N R. Vital Capacity in a Group of College Students, *Arch Int Med* **29** 515 (April) 1922

TABLE 1.—Vital Capacity Readings*

Run ning Num ber	Height	Weight	Sur- face Area	Normal Vital Capacity	Vital Ca- pac- ity Before Race	Per- cent- age of Nor- mal	Vital Ca- pac- ity After Race	Time After Finish	Per- cent- age of Fall of Vital Ca- pac- ity After Race	Vital Capa- ci- ty Calcu- lated from Height	Per- cent- age of Nor- mal
				Calcu- lated from Surface Area							
63	173	62.8	1.76	4.40	3.20	118	4.10	6 min	21	4.25	122
26	175	67.6	1.82	4.55	4.75	104	5.20	20 hrs	0	4.25	109
55	164	55.4	1.60	4.00	4.40	110				3.80	116
76	170	69.4	1.70	4.25	4.25	100	3.95	9 min	7	4.10	101
46	172	57.6	1.63	4.20	3.90	93	3.50	5 min	10	4.20	93
44	167	59.8	1.68	4.20	3.70	88	2.95	7 min	20	3.95	94
29	172	61.2	1.72	4.20	3.95	92				4.20	94
22	172	61.8	1.74	4.25	4.70	108	4.55	6 min	3	4.20	112
18	158	51.2	1.50	3.75	3.20	104	3.40	3 min	12	3.50	112
44	172	63.0	1.76	4.40	4.65	106				4.20	111
74	177	54.6	1.65	4.15	4.20	104	3.40	3 min	21	4.45	97
23	167	52.2	1.58	3.95	4.20	109	3.45	4 min	20	3.95	109
59	172	61.6	1.74	4.25	4.60	106				4.20	110
57	170	65.4	1.76	4.40	3.85	88	2.95	4 min	23	4.10	94
15	160	57.6	1.60	4.00	3.65	91				3.60	101
23	162	57.6	1.62	4.05	3.25	83	2.80	3 min	16	3.70	91
21	162	53.0	1.56	3.90	4.20	108	3.80	1 min	10	3.70	114
7	175	60.4	1.74	4.25	4.95	114	4.45	6 min	10	4.25	114
27	165	61.4	1.68	4.20	4.80	114	3.60	3 min	25	3.85	125
53	165	69.4	1.76	4.40	4.15	95	2.00	4 min	52	3.85	108
50	178	57.2	1.72	4.20	4.50	105				4.50	100
43	170	62.0	1.71	4.25	4.25	87	3.05	2 min	20	4.10	93
60	160	61.4	1.64	4.10	4.10	84	3.25	2 min	6	3.60	93
53	167	55.0	1.62	4.05	2.80	94				3.95	99
11	170	65.0	1.76	4.40	3.10	71	2.70	2 min	12	4.10	76
2	175	60.8	1.74	4.35	6.00	128	4.60	3 min	23	4.35	128
29	177	59.0	1.74	4.25	3.95	91				4.45	89
49	180	63.5	1.88	4.70	5.15	110	4.55	2 min	11	4.60	112
19	177	71.6	1.88	4.70	5.50	117				4.25	126
52	165	55.8	1.62	4.05	4.50	111				3.85	117
6	167	54.4	1.60	4.00	3.25	84				3.95	85
11	177	74.0	1.89	4.75	5.20	110				4.45	117
35	162	54.4	1.58	3.95	3.70	94	2.90	3 min	21	3.70	109
4	172	66.6	1.89	4.50	3.95	88				4.20	94
1	163	66.2	1.74	4.25	4.20	99				3.85	112
8	170	61.2	1.70	4.25	4.50	106				4.10	110
9	163	58.0	1.62	4.05	4.20	104				3.75	112
12	160	60.0	1.62	4.05	4.20	104				3.60	117
12		51.4									
14	170	52.6	1.60	4.00	3.20	83				4.10	81
16	175	65.4	1.89	4.50	2.90	87				4.25	90
17	167	61.8	1.70	4.25	3.25	79				3.95	85
20	162	52.6	1.54	3.85	3.50	91				3.70	95
24		58.6			3.20						
25	165	57.6	1.62	4.05	2.25	80				3.85	85
27	172	64.4	1.76	4.40	4.00	91				4.20	95
23	167	64.8	1.72	4.20	4.20	98				3.95	106
39	159	54.8	1.70	4.25	4.45	105				4.60	97
51	177	57.8	1.72	4.20	4.60	92				4.45	99
54	177	64.4	1.89	4.50	4.40	98				4.45	99
35	177	78.6	1.96	4.90	3.70	76				4.45	83
38	172	79.4	1.94	4.85	4.50	93				4.20	107
41	170	57.6	1.66	4.15	2.40	82				4.10	83
42	159	65.8	1.84	4.60	4.50	94				4.60	94
43	170	61.2	1.70	4.25	4.60	115				4.10	120
45	177	65.8	1.82	4.55	4.60	101				4.45	103
54	182	74.4	1.96	4.90	4.80	98				4.70	102
62	177	69.0	1.86	4.65	4.60	99				4.45	103
65	178	65.4	1.82	4.35	5.05	111				4.50	122
67	170	62.2	1.72	4.20	4.45	104				4.10	109
68	177	69.4	1.86	4.65	4.65	100				4.45	104
69	167	67.6	1.76	4.40	4.60	105				3.95	116
71	173	63.2	1.73	4.45	4.20	110				4.23	113
72	163	61.6	1.74	4.25	3.80	87				4.00	95
75	166	60.4	1.68	4.20	4.10	98				3.90	105
76	170	69.4	1.80	4.50	4.55	101				4.10	111
78	162	62.0	1.74	4.35	4.10	94				3.70	111

* Observations tabulated in the order of finish of the first thirty-four runners.

Height is expressed in centimeters, weight in kilograms, surface area in square meters and vital capacity in liters.

§ The height formula of Hewlett and Jaer-on vital capacity = 50, height minus 4.464

of the lungs in most of the cases fell appreciably. The average fall was 17 per cent, and the average time after the finish of the race that the observations were made was 38 minutes. This fall we believe is due to the physical exhaustion and less effective control of the respiratory muscles rather than to any impediment to the inflow of air into the lung spaces. The latter hypothesis is still possible, although no evidence of congestion of the lungs, such as râles at the bases, was made out on auscultation. In several instances, it was found that the vital capacity reading returned to the original figure a day or so after the race.

PART 2 THE EFFECT OF THE MARATHON RACE ON THE SIZE OF THE HEART

Many observations have been reported on the effect of long distance running or prolonged effort on the size of the heart, but probably because of the varied methods of study, the results have been conflicting. In 1899, Williams and Arnold⁴ studied the hearts in competitors before and after the Ashland-Boston marathon race by means of palpation and percussion. For three successive years, Larrabee and Strong⁵ observed runners who participated in this annual event. These findings were also based on changes in the percussion outline of the heart. They reported a general enlargement in nearly all competitors before the race with a further and more or less symmetrical increase immediately after the race.

In 1909, Boyce and Grier, under the direction of Watson L. Savage,⁶ made fluoroscopic studies of hearts in competitors of the Pittsburgh marathon. The first observations after the effort were made from fifteen to sixty minutes after the completion of the race. Their findings suggested an enlargement immediately following the race, with a reduction in the heart outline one week later. They also concluded that the hearts of successful marathon runners were above the average size.

Boigey⁷ made orthodiagnostic records of competitors before and after a 42 kilometer race and found dilatation of the heart. In the same paper, he noted a contraction of the heart after a 100 meter foot race. Dedickem⁸ examined by palpation and percussion 226 runners before and after a 50 kilometer marathon. He was unable to demonstrate any enlargement of the heart.

4 Williams and Arnold Philadelphia M J **3** 1233 1899

5 Blake, J B , Larrabee, R C , and Strong, L W Boston M & S J **148** 201, 1903

6 Savage, W L , Boyce, J W , and Grier, G W Am Phys Education Rev **15**, No 9 (Dec) 1910, **16**, Nos 1, 2, 3, 4, 5 (Jan , Feb , March, April, May) 1911

7 Boigey Presse med **26** 657, 1921

8 Dedickem Acta Med Scand **53** 738, 1921

On various occasions, Shott⁹ has contended that the heart dilated following exercise. In 1908, Moritz¹⁰ found that the heart shadow, as seen by orthodiagram, failed to enlarge after exercise and that in certain instances, it contracted. This phenomenon was seen in normal and in slightly pathologic hearts. De la Camp¹¹ arrived at the same conclusions as did Hoffmann,¹² who reported that he was unable to determine any dilatation in the normal heart following exertion.

In 1914 Nicolai and Zuntz¹³ studied the effect of exercise on the heart in normal subjects operating a tread-mill. They reported a transverse diameter increase during work and a decrease a few seconds after work. Williamson,¹⁴ in 1915, studied most accurately the effect of stair climbing on the size of the normal and pathologic heart. He measured the transverse diameters on teleoroentgenograms and paid considerable attention to the position of the diaphragm. He was of the opinion that normal and about one half of the pathologic hearts diminished in size after exertion. In the same year, Lee, Dodd and Young¹⁵ showed that there was little difference in the size of the hearts of men who had been rowing two or four years and men who had been rowing more than ten years. One of us, working with Strong,¹⁶ studied the effects of exercise to exhaustion on the normal and abnormal rabbit's heart. The animals were exercised in a tread-mill and the heart size, as determined by the roentgen ray, before exertion was compared with the silhouettes taken at various times following exertion. In most instances, there was a definite decrease in size after effort not only of normal but also of pathologic hearts, and a gradual return to normal after one hour.

In this study of the Boston marathon of April, 1923, we used a standard portable roentgen-ray apparatus with an adjustable vertical plate holder.¹⁷ The equipment was placed on the second floor of the Boston Athletic Association club rooms, close to the elevator and within

9 Shott, T. Verhandlungen des Kongresses fur Innere Med. **9** 448, 1890, Munchen med Wchnschr **55** 952, 1908, Deutsch med Wchnschr (April, 1897) p 220

10 Moritz, F. Munchen med Wchnschr **55** 713 and 1331, 1908

11 De la Camp. Ztschr f klin Med **51** 1, 1903

12 Hoffmann, A. Verhandlungen des Kongresses, f Innere Med **20** 307, 1902

13 Nicolai, G F, and Zuntz, N. Berl klin Wchnschr **51** 821, 1914

14 Williamson, C S. Am J M Sc **149** 492, 1915

15 Lee, R I, Dodd, W J, and Young, E L. Boston M & S J **173** 499, 1915

16 Gordon, B, and Strong, G F. Studies on the Rabbit's Heart, Arch Int Med **32** 510 and 517 (Oct) 1923

17 The films were taken at a distance of 3 feet and a current of 10 millimeters was used, backed up by a 4½-inch spark gap, with an exposure of five seconds. The equipment was supplied by Kehlenback and Saxby, agents for the Wappler Company in Boston.

100 yards of the finish line. A convenient dark room was at hand to facilitate the change of films. Our technic consisted of immediately bringing the runners from the street and having them stand in front of the plate holder. In some instances, the men were so completely exhausted that it was necessary to give them assistance in order to maintain an upright position during the procedure. Without delay, the picture was made, and in most instances the entire operation was completed within three minutes after the runner crossed the finish line. The competitors then rested for about one hour and returned to the stand for a second roentgen-ray film. A number of men came to the roentgen-ray department of the Peter Bent Brigham Hospital the next day or some days later, when other heart plates were taken. It was unfortunately impossible to obtain roentgenograms before the race for comparison, but this did not prevent certain obvious deductions from our studies.

The results are charted in the accompanying Table 2. It will be noticed that immediately after the race (Period A) all the hearts were rather small, none was dilated. In six cases examined from one to one and one-quarter hours later, the second roentgenogram (Period B) showed that the heart must have been contracted about 1 cm., for the transverse diameter in B was distinctly larger than in A. There were four other instances in which the change amounted to only a few millimeters, but these were considered to be within the limit of technical error. Further roentgen-ray data were obtained in five cases, from one to sixteen days after the race, for purposes of comparison (Period C). All of them showed a further increase over the dimensions obtained about one hour after the race, and one showed an increase of 11 cm. although none had been previously noted.

In this study, due consideration was given to the position of the diaphragm as suggested by Williamson,¹⁴ Bordet,¹⁸ and others. It is known that a high diaphragm produces an increased transverse diameter of the heart shadow for purely mechanical reasons. In Table 2 are charted six instances in which the position of the diaphragm was different in the various plates of the same person. In four of them, there was a gradual increase in the size of the heart after the first roentgenogram was taken. In two, there was no appreciable change. The increase occurred in three instances with the diaphragm lower (Nos. 63, 60, and 22) and in one with the diaphragm higher (No. 11). This indicates that despite the higher position of the diaphragm immediately after the race which might have increased the transverse diameter of

18 Bordet, E. Arch des mal du coeur, February, 1923, p. 108.

the heart, apparently the hearts were smaller than they were later when the diaphragm descended, in a word, the position of the diaphragm did not alter the general deductions that might be drawn from these observations.

A further control on the roentgen-ray measurements appears in comparing the transverse diameter of the chest of the same persons in

TABLE 2—*Roentgen-Ray Measurements of the Heart and Chest*

Running Number	Order of Finish	Time Elapsed Between Finish of Race and Taking of Roentgenograms	Transverse Diameter of Heart	Internal Transverse Diameter of Chest	Cardio-thoracic Ratio Percentage	Position of Diaphragm
63	1	A 1½ min	12.5	32.9	38	—
		B 85 min	13.3	32.5	41	Lower
		C 29 hrs	14.0	34.5	41	
26	2	A 2½ min	13.2	32.0	41	Equal
		B 80 min	14.2	32.1	44	
55	3	A 2 min	11.5	31.4	36	—
70	4	A 1¼ min	14.4	31.0	43	
		B 87 min	14.2	31.2	46	Higher
46	5	A 3½ min	14.4	31.4	46	—
		B 88 min	14.5	31.9	45	
44	6	A 5 min	13.3	30.2	44	—
		B 63 min	12.9	30.5	42	
39	7	A 5 min	11.7	29.8	39	—
		B 60 min	11.9	30.3	39	
22	8	A 2 min	12.7	30.5	42	—
		B 73 min	13.6	32.6	42	
		C 17 hrs	14.4	34.5	42	
18	9	A 4 min	13.3	29.3	45	—
		B 62 min	13.2	29.6	45	
74	11	A 2 min	16.2	33.8	48	—
		B 64 min	16.9	34.2	50	
33	12	A 2 min	12.2	29.2	42	—
		B 65 min	13.1	29.8	44	
		C 16 hrs	15.6	29.5	53	
59	13	A 2½ min	13.1	33.5	39	—
		B 67 min	13.2	34.7	38	
57	14	A 2¾ min	13.0	32.4	40	—
15	15	A 2 min	12.7	33.2	38	
23	16	A 1½ min	12.6	30.4	41	—
		B 57 min	12.6	30.4	41	
7	18	A ¾ min	14.2	32.1	44	—
		B 62 min	14.4	32.5	44	
		C 16 days	15.5	32.0	36	
37	19	A 2 min	12.3	31.1	40	—
		B 69 min	13.8	31.6	44	
53	20	A 5 min	12.7	33.7	38	—
60	23	A 2 min	11.5	28.3	41	—
		B 70 min	12.5	28.5	44	
58	24	A 1¾ min	10.9	30.3	36	Lower
11	25	A 3 min	11.5	29.3	39	
		B 60 min	12.5	29.2	43	Higher
2	26	A 2 min	12.7	32.3	39	—
		B 99 min	13.7	32.2	43	
		C 18 hrs	13.9	31.7	44	

different plates. With three exceptions, Nos 22, 59, and 63, the difference was under 0.6 cm. This indicates that from a technical point of view the heart measurements were obtained with a satisfactory degree of accuracy. By dividing the transverse diameter of the heart by the internal transverse diameter of the chest the so-called cardiothoracic

ratio may be obtained which, according to Danzer,¹⁹ in normal people should not exceed 52 per cent. The figure is applicable only when obtained from a heart plate taken at a distance of 7 feet. Our readings were made from plates taken at a distance of 3 feet. One can readily see that the hearts were on the whole small or normal. Comparing the cardiothoracic ratio of roentgen-ray plates taken at 3 feet with those taken at 7 feet in a group of normal persons, we found that the former was 3 per cent less than the latter, therefore, the upper limit of normal in our measurements would be 49 per cent. From our table, one may conclude that the marathon runners showed no enlargements of the hearts, for in only one instance (Runner 33) was the ratio appreciably above normal at any time.

PART 3 BLOOD PRESSURE AND GENERAL CONSIDERATIONS

Due to certain difficulties in the work, only a limited number of blood pressure measurements were made. The pressure was taken either on the right or left brachial artery by means of a Tycos manometer, with a cuff 12 cm broad. The reading was made on decreasing contrapressure. The systolic pressure was easily determined, while the diastolic was difficult to obtain, because the sounds were of decreasing intensity before the diastolic contrapressure was reached and were present a long time in the infradiastolic zone, thus the characteristic feature of the changing quality of the sound was not easily ascertained. This refers to the readings made by the auscultatory method. There were almost similar features to deal with in the use of the palpitory method, the thumb palpating the brachial artery just below the armlet. In the present observations, both methods were employed simultaneously, and often the doubt resulting from one was cleared up by employing the other. Furthermore, in some instances, we were helped by observing the oscillations of the small spring manometer, thus making use, in a rough way, of the oscillatory method. In a few cases, however, no definite figure could be ascertained.

We never found a so-called "gap" or even a "valley" in the infrasystolic zone. The intensity of the arterial sounds increased progressively, and this, according to the recent work of Barbier²⁰ indicates an energetic expulsion of the blood throughout the cardiac systole. The loud blowing character of the arterial sound that was found in the infrasystolic zone and the increased resonance of the sounds around and above the diastolic point, are, according to the same author the result of a hypertonic state of the arterial wall (vasoconstriction, hypersympatheticotonus), but they can also be due, at least partially, to increased pulse pressure.

19 Danzer, C S Am J M Sc 157 513, 1919

20 Barbier, J La methode auscultatoire dans l'exploration cardiovasculaire, These, Lyon, 1921

The blood pressure readings are given in Table 3. In most instances, immediately after the race, the systolic pressure was found to be about normal, on the other hand, the diastolic pressure was definitely reduced, the ratio, of systolic to diastolic, which ranges normally from 14 to 17, being thus increased. During the following hours, it seems that first the systolic pressure fell and then both the systolic and diastolic rose together to normal. It is quite apparent that our data are incomplete concerning blood pressure changes. This subject and observations on the tonus of the blood vessels need further investigation.

We had occasion to talk with the men during the examination (or at a later date) about the symptoms they experienced during the race. Quite a number remarked about the pain in the upper part of the

TABLE 3.—*Blood Pressure Examinations*

Running Number	Arrival Number	Blood Pressure (in Mm of Mercury) Up to 10 Min After the Finish			Blood Pressure (in Mm of Mercury) At Various Times After the Race		
		Maxi- mum	Mini- mum	Time	Maxi- mum	Mini- mum	Time
63	1	110	58	4 min	118	72	30 hours
46	5	130	70	9 min	—	—	—
22	8	—	—	—	148*	92*	1 hr 40 min
18	9	—	—	—	108	58	1 hr 30 min
40	10	130	58	8 min	—	—	—
59	13	—	—	—	98	72	1 hr 15 min
57	14	134	70 or 50	7 min	—	—	—
53	20	110	84	8 min	—	—	—
48	22	130	54	8 min	—	—	—
60	23	132	80	5 min	—	—	—
2	26	150	66	7 min	126	86	22 hours
19	29	120	58	10 min	—	—	—
32	30	—	—	—	92	62	45 minutes
77	32	120	78 or 58	9 min	102	82	1 hr 10 min
25	—	108	58	—	—	—	—
8	—	112	60?	—	106	72	45 minutes
54	—	130	88	—	—	—	—

* Runner 37 years old.

right side of the abdomen which appeared after the first two or three miles. Others referred to a slight nausea that came later in the race. These discomforts usually disappeared after slowing the speed or walking for a short distance. Most of the men at some time or another experienced pain or stiffness in the muscles of the legs and blisters on the soles of the feet. They felt that their position at the finish line depended largely on the condition of their legs and that all other discomforts were of minor importance. None complained of any difficulty in breathing or pain in the chest. When asked why they could not run faster at the end of the race, they all said that their "legs just would not move any faster." They insisted that dizziness did not enter into it.

On examination, no râles were heard in the lungs, and the liver edge could not be felt. It was thought that one of these positive findings might be present as evidence of circulatory embarrassment, but on

considering the entire picture that a marathon runner presents, we came to the conclusion that given a normal heart, the most important point in summary training is that of the legs rather than the wind

SUMMARY

1 The average vital capacity of the lungs in marathon runners was normal, which indicated that prolonged vigorous training did not increase the breathing space of the lungs

2 There was a fall of 17 per cent in the vital capacity immediately following the race, and this returned to normal in twenty-four hours

3 There was no important relationship between the vital capacity of the lungs and the order in which the runners finished

4 The size of the heart as determined by the roentgen ray in marathon runners is not enlarged. This indicated that many years of the most vigorous physical effort did not produce cardiac hypertrophy

5 Immediately following the race, it seems that there was a temporary decrease in heart size, gradually returning to normal in about one day

6 No "gap" was found in the auscultatory curve of the brachial artery. The systolic pressure immediately after the race was normal while the diastolic was distinctly diminished. It is suggested that shortly afterward the systolic pressure fell, whereupon both pressures slowly rose to normal

GASTRIC SECRETION, GASTRO-INTESTINAL MOTILITY AND POSITION OF THE STOMACH

IN A GROUP OF 250 CHILDREN OF THE LYMANHURST SCHOOL

C B WRIGHT, MD

MINNEAPOLIS

There is a large amount of literature on the position of the stomach in the adult and in the suckling, but not so much on its position in older children. Previous to the use of the roentgen ray and the opaque meal much work was done by percussion and air or gas distention on the cadaver, but with the use of the roentgen ray it was found that these observations did not give us an accurate knowledge of the position of the stomach and colon in the living upright person, and from the clinical standpoint, this, of course, is the important consideration.

DeBuys and Henrique,¹ in a study of infants and young children, did not find an adult type of stomach up to the age of 3 years. They also first noted active peristaltic waves in the stomach of a child at the age of 4 months. Petri,² in a series of observations on fourteen infants' stomachs, found that although the major portion of the meal passed into the intestines in from one and a half to two and a half hours, the stomach did not completely empty until from four to seven hours. Richard R. Smith³ examined 109 female children varying in age from birth to 13 years. Only twenty-four of these were studied with the roentgen ray. No definite measurements were given, but he found no children with the hook formed stomach, up to the age of 3 years. He concluded that the visceroptotic habitus is found in children of the frail type, and that prolapse of the liver, kidney, stomach, and colon is seen only in rare instances in children under 12 years of age.

Butler, in 1910, reported observations on a series of 155 children, fifty girls and 105 boys. His conclusions were that evidences of enteroptosis are observable throughout childhood, but more often at puberty. In the first days after birth palpable liver and kidneys are common. Beyond the first year up to later childhood, palpable livers and displaced

1 De Buys, L R, and Henrique, Adolph. Effect of Body Posture on the Position and Emptying Time of the Stomach, Am J Dis Child 15:190 (March) 1918
2 Sever, James Warren. The Position of the Stomach in Children, Arch Pediat 31:38, 1914

3 Petri X-Ray Observations on the Lower Colon, Jahrb f Kinderh 82:87, 122

Smith Richard R. A Study of Children with Reference to Enteroptosis, J A M A 58:385 (Feb 10) 1912

stomachs are exceptional, although signs of the habitus are evident in some of the children. The active ptoses he believes are seen at the period of puberty. No measurements are given, and roentgen-ray study was only partial.

Sever, in 1914, reported a series of examinations in eighty-three children, twenty-three of which were boys. The ages varied from 4 to 18 years. The children were normal in height, weight and nutrition, according to Holt's figures. He concluded that general condition and body weight had little to do with the position of the stomach. He also found the index of Bisher and Lenhoff, which is determined by dividing the jugulo pubic distance by the waist measure taken just below the ribs and multiplying by 100, gave little indication of the position of the viscera. He noted that of the eighty-three children, two showed the lower pole opposite the fourth lumbar vertebrae, and nine showed it at the level of the crests, and that in forty-nine the lower pole was well below the crests, sometimes as much as 3 and 4 inches (7.6 and 10.1 cm.). No exact measurements are given, except of extreme types.

He found that the shape of the stomach varied considerably, although the most persistent form was of the sink drain type. There were few steer horn shaped stomachs. None of these were seen in the position regarded as normal for the adult. Many were seen in the midline, but many were to the left, apparently resting well within the iliac fossae. He found only one pathologic case—that of a child with a dilated colon and constipation.

At the Lymanhurst school opportunity was offered for the study of a group of children whose ages varied from 6 to 7 years. Two hundred and fifty children were examined in a routine manner as follows. The children were given in the morning on an empty stomach one glass of water and one slice of bread.¹ Approximately forty-five minutes later the meal was aspirated and studied. They were then given about 300 cc of cereal and 2 ounces of barium sulphate and at intervals varying from three and a half to six hours later they were examined with the fluoroscope from the standpoint of motility. They were then given approximately 450 cc of buttermilk and 2 ounces of barium sulphate, their stomachs studied as to form, and plates were taken both lying and standing, the tube parallel to the umbilicus and 39 inches (99 cm.) from the plate.

The data obtained on the following points will be considered in this paper:

1 A brief record of the results of the Ewald meal.

2 The position of the stomach related to a line drawn at the level of the iliac crests.

3 The measurements of the intercostal angle and its relationship to the position of the stomach

4 The palpability of the liver, kidneys and spleen and the motility of the stomach

5 A report of two cases of dilated colon and constipation found in the series

In a study of the children in this group from the standpoint of height, weight and general nutrition, Dr Richard Scammon found that they compared favorably with an unselected group, according to the general standards used.

The results from the Ewald meal varied from a few cubic centimeters to 125 cc in amount, there apparently being no uniformity. Considerable variation in the actual time of taking the meal and tech-

TABLE 1—*Free Hydrochloric Acid*

Age Period 6-17	No Cases 230	Maximum Acid, Percentage 55	Minimum Acid, Percentage 0	Males, Average 20-30	Females, Average 20-30	Both Males and Females 20-30

TABLE 2—*Total Acidity*

Age Period 6-17	No Cases 230	Maximum Acid, Percentage 80	Minimum Acid Percentage 7	Males, Average 40-50	Females, Average 40-50	Both Males and Females 40-50

nical difficulty in completely evacuating the stomach, particularly in patients of this age, undoubtedly are factors in this variation.

Figures 1 and 2 are self explanatory and show the range of free hydrochloric acid and total acidity. The findings portrayed in these illustrations are given in Tables 1 and 2. In the series of 230 cases in which this was plotted, the free hydrochloric acid ranging from 0 in four cases to 55 in one, the average being 40-50. The curves of free and total acidity follow each other up and down in marked uniformity.

In the four cases with no free hydrochloric acid, only two could be subsequently examined. Of the two examined about one year later, one showed a free hydrochloric acid of 18. The other still showed complete absence of free hydrochloric acid.

In the study of the position of the stomach, a line drawn between the iliac crests was used as the zero point. At first I tried to use a marker at the umbilicus, but I found it inaccurate. Roughly, however, in these observations the level of the umbilicus was found to correspond well with the iliac crests in the standing position.

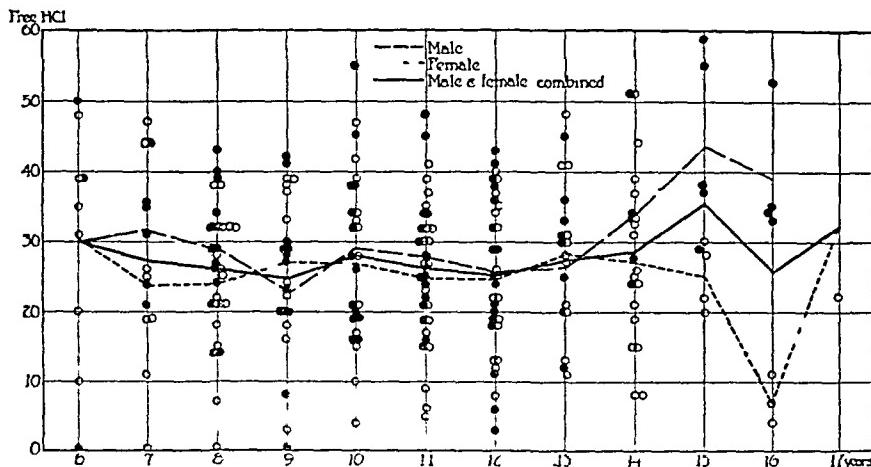


Fig 1.—Free hydrochloric acid findings. The figures running vertically represent the free hydrochloric acid. The figures below represent age periods of the children.

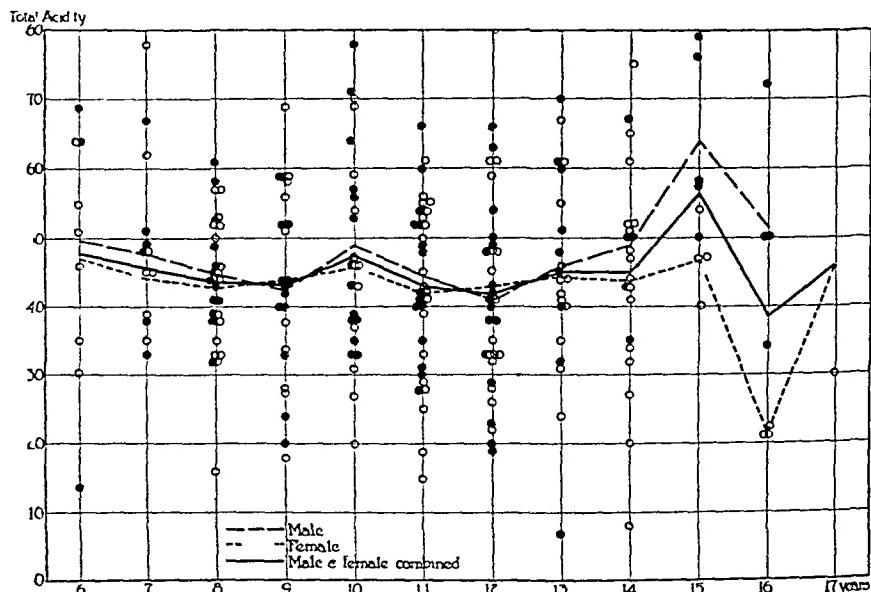


Fig 2.—Total acidity findings. The figures running vertically represent the total acidity. The figures below represent age periods of the children.

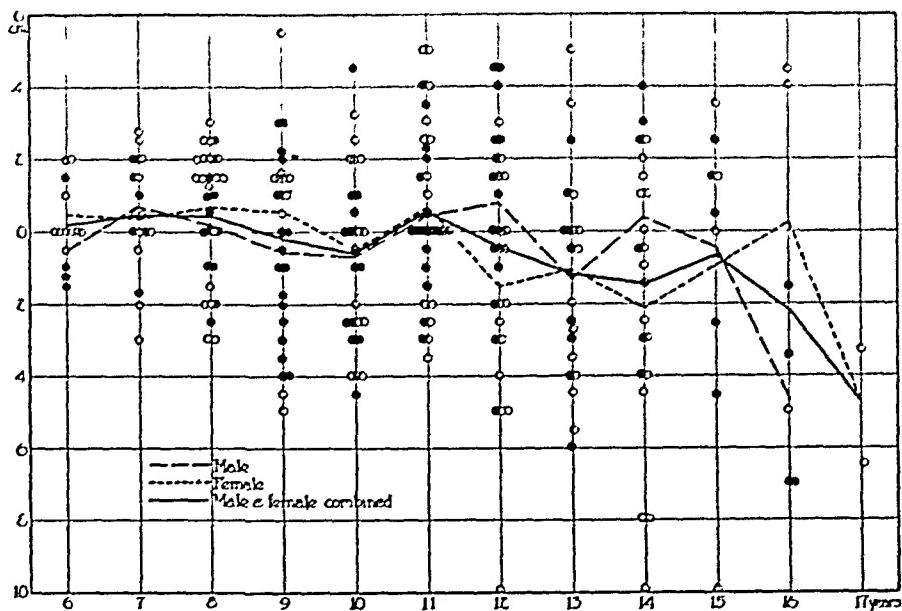


Fig. 3.—Position of the lower pole of the stomach, zero being taken as the line drawn to the iliac crests and the figures on the right being above and below the crests (in centimeters). The figures below are the ages of the children in years. In this summary, the children aged 16 and 17 were not counted because there were so few of them.

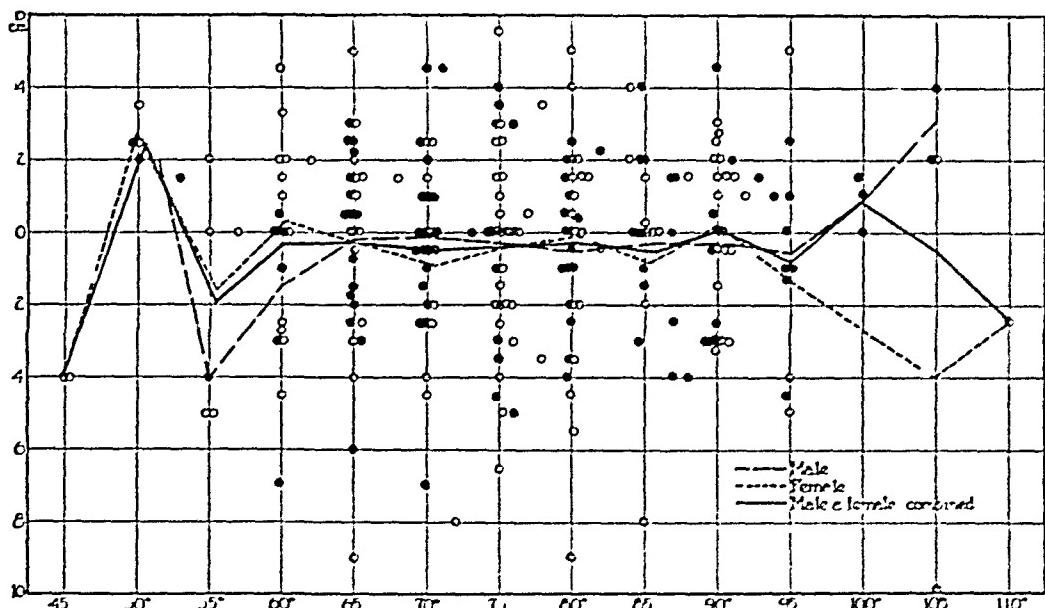


Fig. 4.—Relationship between the position of the lower pole of the stomach and the intercostal angle. The figures on the right represent the distance above and below the line drawn from the iliac crests which is taken as zero, and the intercostal angle in degrees.

Figure 3 shows the position of the stomach (also shown in Table 3), O being the crests and the distance above and below in centimeters, for the various ages from 6 to 17 years inclusive, the highest being nearly 6 cm above the crests, the lowest 10 cm below the crests, of which there were three. The average lies close to the iliac crests with a slight tendency downward, after the age of 11. Yet, it is an exceedingly uniform variation in both directions. From this chart, although there are some very low stomachs, it would be difficult to determine where the position becomes pathologic. One might call the group below 6 cm pathologic, as they seem to stand more in a class by themselves. These are all over 13 years. However, is it much more extreme relatively at this age than a stomach 5 cm below at the age of 9 or 3 cm below at the age of 7?

TABLE 3.—Position of Stomach with Distance from Iliac Crests to Lower Pole

Age	Male		Female		Both	
	Average Distance Cm	Number of Cases	Average Distance Cm	Number of Cases	Average Distance Cm	Number of Cases
6 to 15, inclusive	-0.54	105	-0.88	130	-0.27	235
6 to 11, inclusive	-0.11	70	-0.33	82	+0.22	152
12 to 15 inclusive	-0.21	35	-1.47	48	-0.84	83

TABLE 4.—Iliac Crest to Lower Pole of Stomach with Intercostal Angle

Both Male and Female				Male				Female			
Average Angle	Average Distance to Lower Pole	No Cases	Average Angle	Average Distance to Lower Pole	No Cases	Average Angle	Average Distance to Lower Pole	No Cases			
77.7	-0.49	243	77.8	-0.18	109	76.0	-0.89	134			

In the total series, 101 cases were above the iliac crests, or 42 per cent, 103 cases, or 42 per cent, were below the crests, and thirty-nine cases, or 16 per cent, were at the iliac crests.

In measuring the intercostal angles, I marked the costal margins with a pencil and then transferred it to tracing paper and measured the angle. The intercostal angle is often used clinically as an indication of the position of the abdominal viscera. In Figure 4 the relationship between the position of the lower pole of the stomach measured from the iliac crests and the width of the intercostal angle is shown (Table 4). The intercostal angle was seen to vary from 45 to 110 degrees. The average position of the stomach seemed to bear no relationship to the intercostal angle, as one might expect. However, no high stomachs were found in cases with narrow costal angles, and no low stomachs in the cases with extremely wide angles. But, in the cases between 55 and 95 degrees, there appears to be no definite relationship. For instance, at the angle of 65 degrees we have cases varying from 5 cm above to

9 cm below, at 80 degrees, from 5 cm above to 9 cm below, and at 55 degrees, from 2 cm above to 5 cm below. This seemed to be equally true of males and females, the curves running quite uniformly for both sexes.

In order to show graphically the position of the stomach at the various age periods, outlines of the stomach were superimposed. The outlines first being marked on the roentgen-ray plate and transferred to a sketch of the pelvic and lumbar skeleton, the two fixed points used being the vertebral column and a line drawn between the iliac crests.

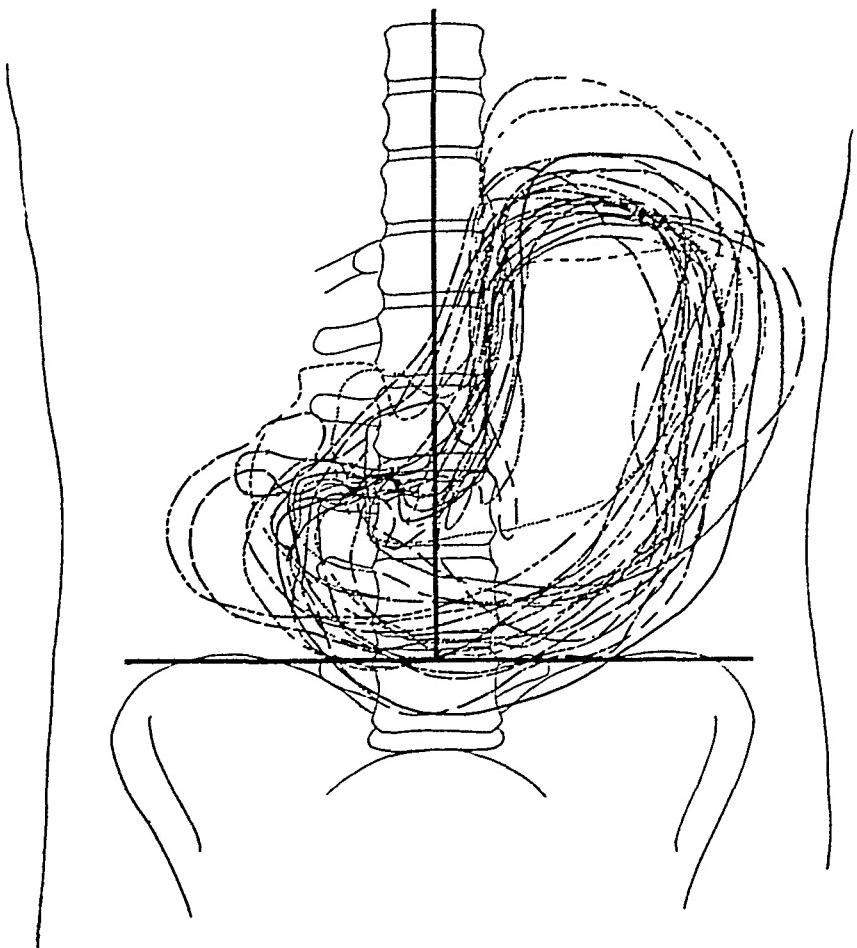


Fig. 5.—The outlines of the stomachs of twenty children at the ages of 6 and 7, superimposed. The fixed lines are the middle of the vertebral column and the crests of the ilium, showing the stomach somewhat farther to the right than in later childhood, and much less variation in the position of the stomach. The general shape of the stomach varies from the sink drain to the very blunt hook.

Twenty cases were used in each sketch and the age periods 6 and 7 were grouped because there were not cases enough to make twenty of either age group, then 8, 10, 12 and 14. With each composite group is a sketch showing the four most common variations.

As the age increases there is apparently a much greater variation in outlines and also in position, both in relation to the two fixed lines—

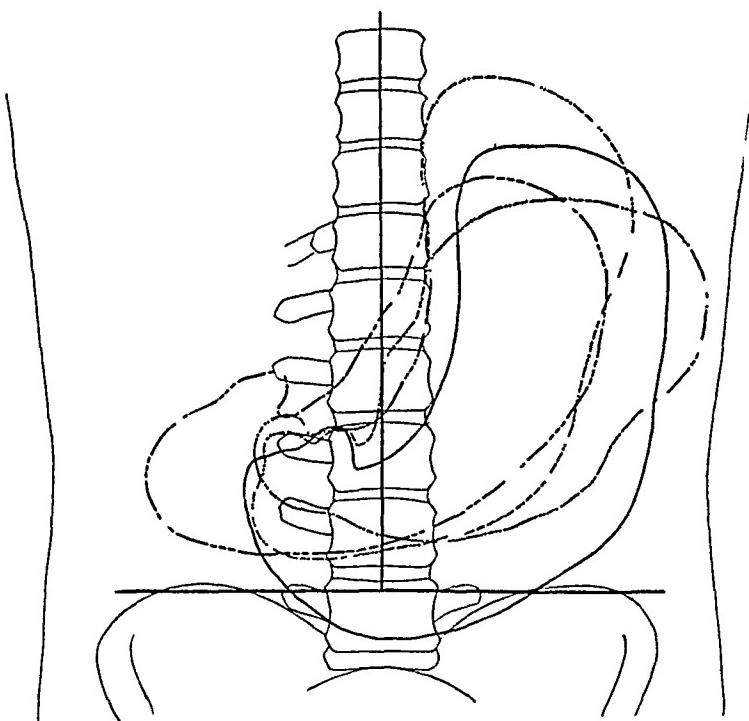


Fig 6—The four extreme outlines selected from Figure 5

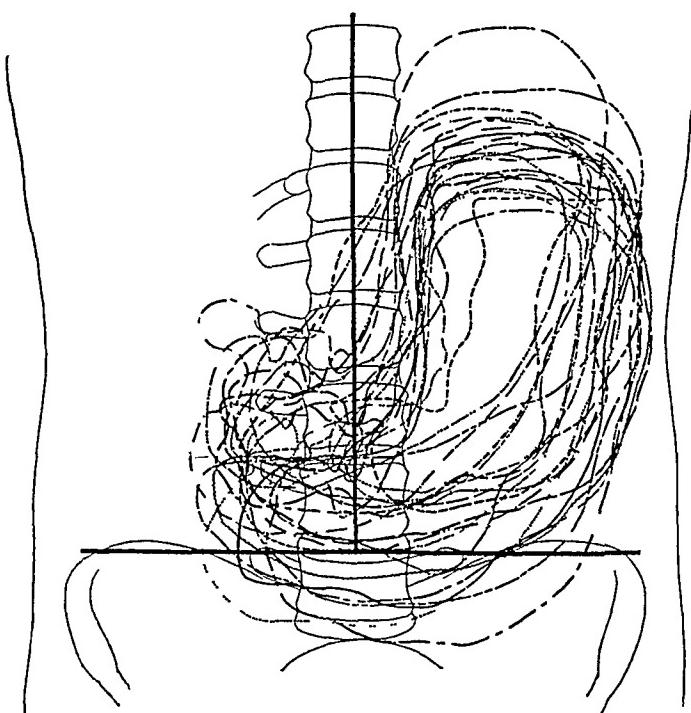


Fig 7—A composite group made the same as in Figure 5, showing more variation in the position of the stomach at the age of 8, an appreciable tendency to the hook form and more variation in the type

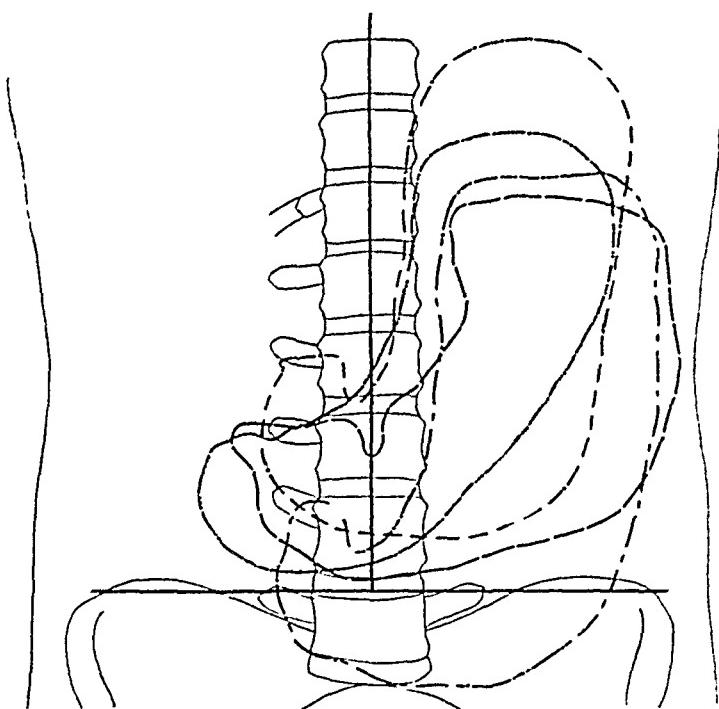


Fig. 8.—The four extremes of Figure 7

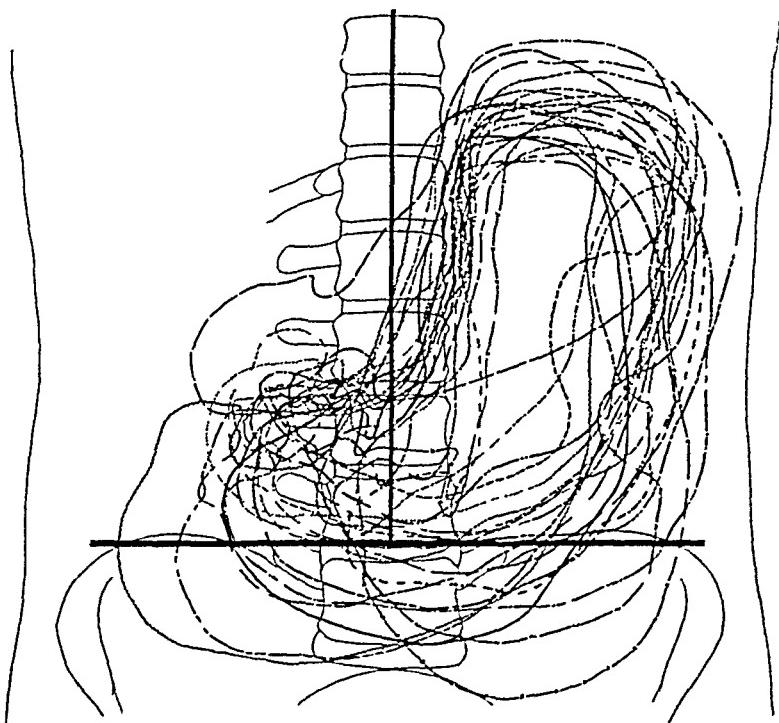


Fig. 9.—The outlines from a group of 10 year old children, showing more variation in type than in the previous ages. The stomach as a whole apparently comes more to the left and generally is more nearly the hook type.

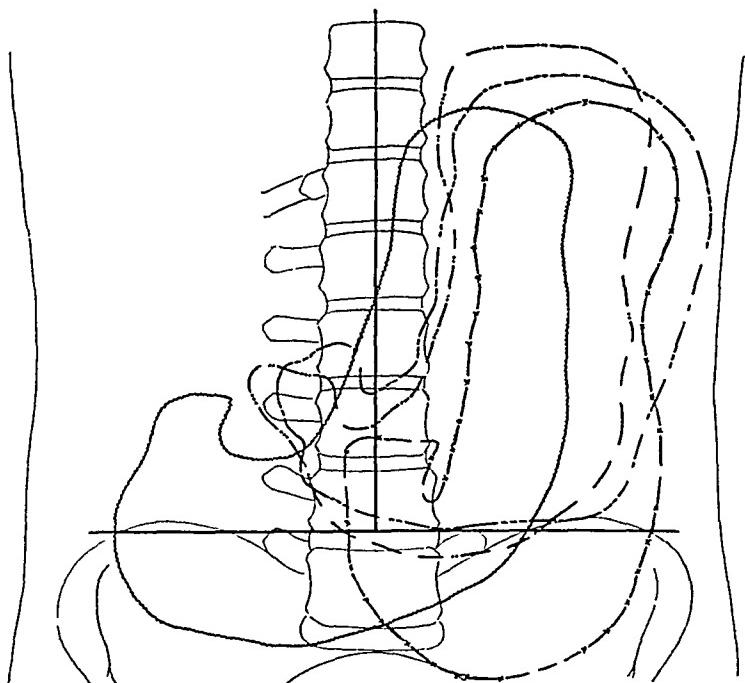


Fig 10.—The four extremes of Figure 9

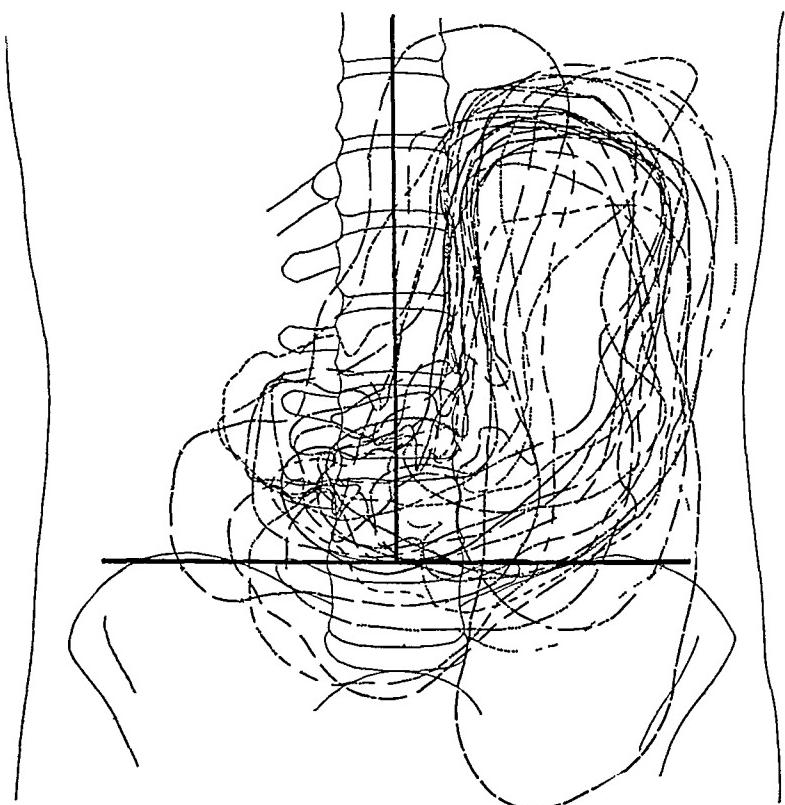


Fig 11.—A group of 12 year old children, showing a general tendency to lower stomach, and more definite hook form and still wider variation in the outlines of the stomach

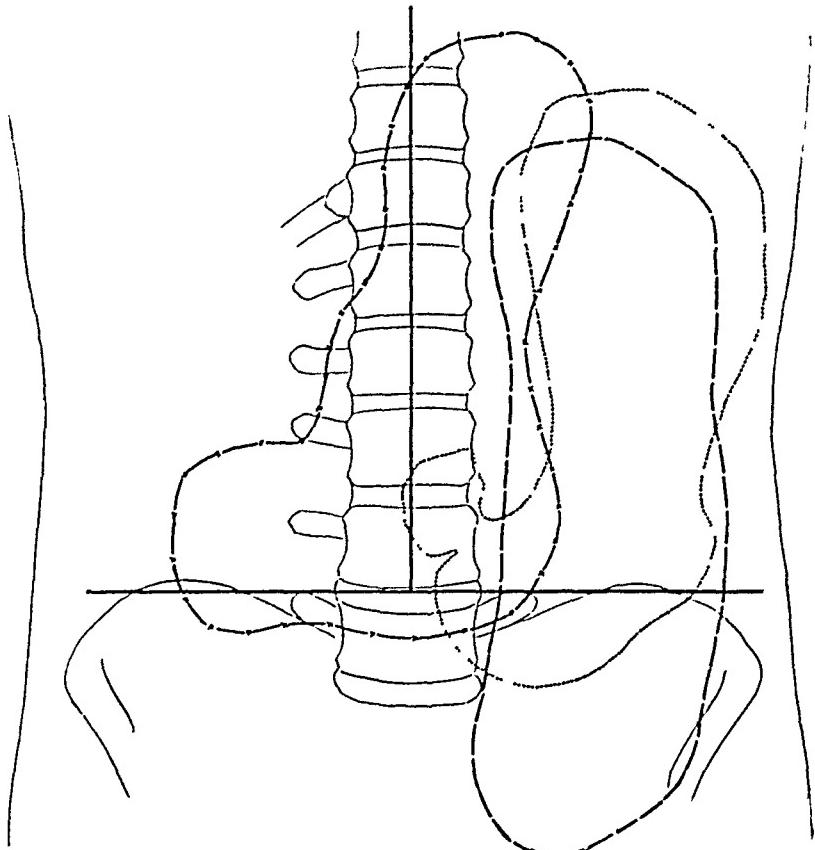


Fig. 12.—The three extremes of Figure 11. The one farthest to the right is the highest.

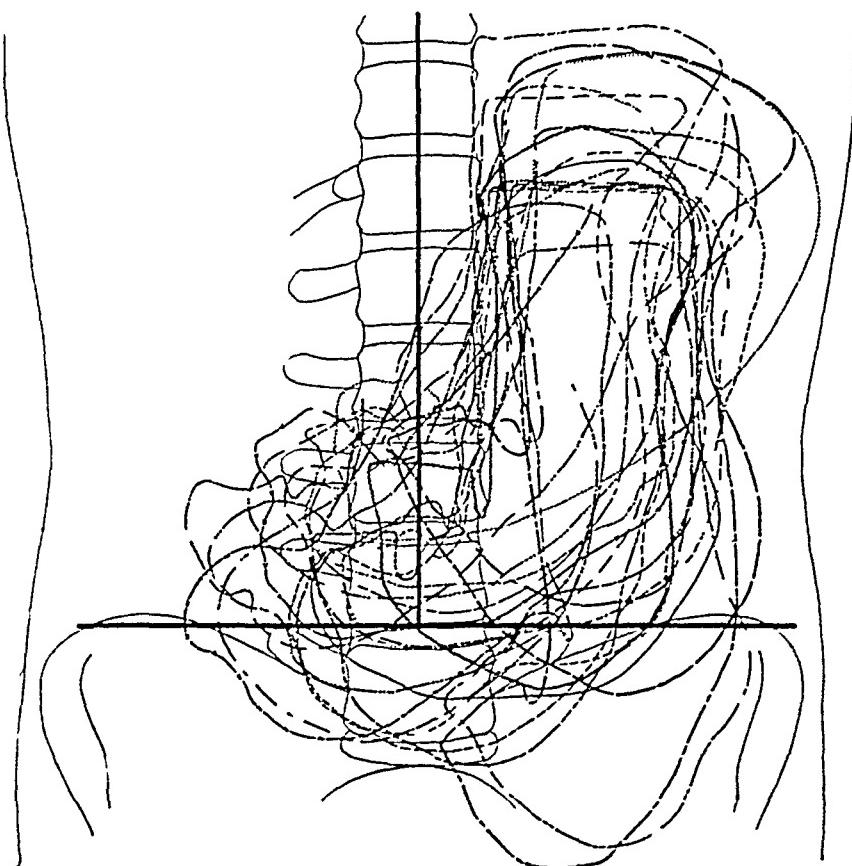


Fig. 13.—A group of 14 year old children, showing still more variation in form, lower stomachs and rather unformed hook shape.

the iliac crests—and the vertebral column. In the 6 and 7 year group there seems to be a closer approximation of outlines with more tendency to the sink drain stomach than at older periods, the sharp hook definitely becoming the characteristic type at the age of 12.

In 243 cases, the liver, kidneys or spleen were palpable in thirty-three cases. The ages in this group of thirty-three varied from 6 to 15 years, and the number at each age period was as follows: age 6, one case; age 7, three cases; age 8, five cases; age 9, two cases; age 10, four cases; age 11, three cases; age 12, five cases; age 13, five cases; age 14,

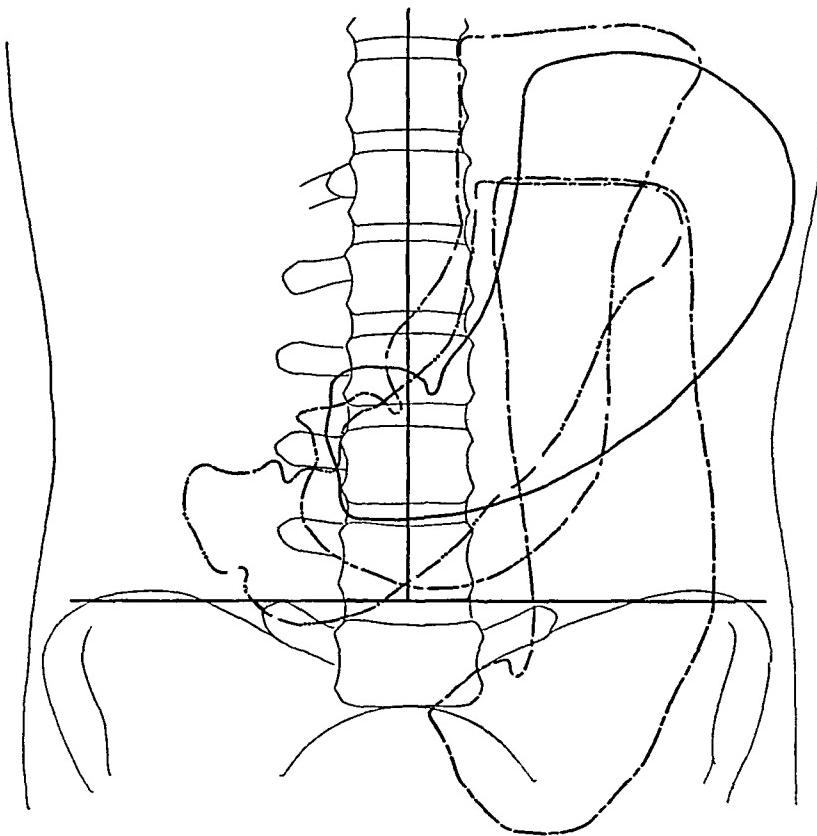


Fig. 14.—Four extremes taken from Figure 13

one case, and age 15, three cases, showing a general distribution among the various ages. In these thirty-three cases, the stomach was below the iliac crests in fifteen, or 47 per cent. In the whole group of 243 cases, in 101, or 42 per cent, the stomach was below the crests, showing too slight a relationship between the palpability of these organs and low stomach to be of any clinical significance. The average costal angles in the thirty-three cases was 72 degrees, the average costal angle for the whole series was 76 degrees. This again shows a slight relationship between the narrow costal angle and the palpability of the liver, spleen and kidneys in this group.

In twenty-three cases, the liver was palpable. In four cases, the spleen was palpable. In eleven cases, the right kidney was palpable. In three cases, both the liver and kidney were palpated. In none of the cases were the liver, right kidney and spleen all palpable in the same case. The left kidney was palpated in none of the cases. There were seventeen females and sixteen males in the series with right kidney, liver or spleen palpable. The right kidney was palpable in eight females and three males. The spleen was palpable in one female and five males. The liver was palpable in eight females and fourteen males.

In this series, there were two cases of dilated colon associated with constipation—one that of a girl aged 13, the other a boy aged 9, both unrecognized before, both gave a history of constipation dating from birth with attacks of more marked constipation requiring enemas and purgatives.

SUMMARY

In children from 6 years to 15 years, the free hydrochloric acid and total acidity is apparently the same as in adults. Absence of free hydrochloric acid was found in four cases of the 250. In two of these cases examined one year later, one showed no free hydrochloric acid, and the other showed a small amount of acidity.

The position, size and shape of the stomach varies widely at all ages from 6 to 15, showing a great variation as puberty is approached. The sink drain type of stomach is more common in younger children, the sharp hook in older children. In 42 per cent the stomach was above the crests of the ilium, in 42 per cent below the crests and in 16 per cent at the crests.

There was little relationship if any between the intercostal angle and the position of the stomach. This also holds true for the position of the liver, right kidney and spleen. Palpable liver and right kidney is common in children of all ages.

In this group of cases, there was found no difference in the gastric chemistry, motility or costal angles between males and females. The position of the stomach was the same up to the age of 11, when there was an appreciable tendency to lower stomachs in females than males. In regard to the palpability of the abdominal viscera, there was practically an equal distribution of palpable abdominal organs between the sexes, seventeen females and sixteen males. The right kidney was felt much more frequently in females, the liver and spleen more frequently in males. Two cases of dilated colon were found which had previously been unrecognized, both in cases having constipation from birth. Seven found one in eighty-three cases, indicating that dilated colon is found in approximately 1 per cent of children. Undoubtedly

all cases of constipation dating from birth should be carefully studied with this condition in view. The motility of the stomach and intestines is greater in children than in adults. This seems to be especially true of the colon.

CONDUCTION CHANGES ACCOMPANYING PERICARDIAL EFFUSION

WITH A CONSIDERATION OF A LOCAL CIRCULATORY FACTOR
IN HEART BLOCK¹

LESLIE T GAGER, MD

NEW YORK

To the effect of pericardial effusion on heart function scant attention has been paid by pathologic physiologists, while clinical emphasis has been directed toward those external manifestations—chiefly the manner and degree of the extension of the limits of cardiac dulness—which provide essential means for the diagnosis of accumulation of liquid in the pericardial cavity. Moreover, the picture is so frequently complicated by a concomitant infection and by inflammatory lesions in the heart muscle or valves that the intrinsic effect of the effusion is obscured. Thus MacKenzie¹ dismisses the subject by stating that he has "never found any very serious embarrassment of the heart from extensive pericardial effusion, the reason being probably that while the normal pericardium is a more or less inelastic bag, with the inflammatory invasion it becomes distensible, and therefore able to accommodate an enormous amount of fluid with little embarrassment to the heart."

On the other hand, Calvert,² in 1907, found marked compression of the heart and its vessels in two cases of large effusion into the pericardium, and on the basis of these anatomic findings discussed the circulatory changes that might be expected under the conditions of altered pressure. Thomas Lewis,³ in 1910, from studies on cats, concluded that "the heart is peculiarly susceptible to the changes of pressure external to it," finding that a rise in intrapericardial pressure of 1 mm of mercury lowered systemic pressure on an average of from 8 to 9 mm of mercury. More recently, Kuno⁴ has studied in dogs the mechanical effect of liquid in the pericardium on the functions of the heart, and he found that circulation ceased when intrapericardial pressure equaled venous pressure, a confirmation of Calvert's deductions. As might be expected, small increases in intrapericardial pressure brought corresponding decrease in cardiac output and arterial tension, up to a certain threshold, beyond which a distinct fall occurred.

* From the Cardiac Clinic of the New York Hospital

1 MacKenzie, Sir James Disease of the Heart, Ed 3, London, 1918, p 283

2 Calvert, W J Bull Johns Hopkins Hosp **18** 403 (Oct) 1907

3 Lewis, Sir Thomas J Physiol **37** 213 (Aug 12) 1908

4 Kuno, Y J Physiol **51** 221 (Sept 12) 1917

To these scattered observations of pericardial pressure effects, we wish to add the clinical record of a man with a large pericardial effusion, accompanied by a well marked depression of conductivity of the bundle of His, which was readily converted by vagus pressure into 2 1 auriculoventricular block. These phenomena disappeared at once after the tapping of 500 c.c. of pericardial liquid. A further point of interest was a definite hypertension, which fell steadily until normal limits were reached and maintained.

REPORT OF A CASE

History—J. R., a man, aged 57, was admitted Feb. 23, 1921, to the New York Hospital, in the service of Dr. Lewis A. Conner. The chief complaint was shortness of breath and heaviness in the abdomen. The family history was irrelevant, and the patient recalled no childhood or adult infections. His health had been excellent until five months before admission when he awoke in the middle of the night with difficulty in breathing. With remissions from time to time, this dyspnea continued to progress, it was always relieved when the patient assumed an upright position.

Physical Examination—This disclosed an orthopeic, sparely nourished elderly man, with moderate pallor, puffiness under the eyes, and edema of the hands, scrotum and lower part of the legs. The pupillary reactions were normal, the knee jerks active. The jugular veins were not distended. The chest was emphysematous, at both bases, tactile fremitus was diminished, with dulness and diminished breathing. The apex impulse was not seen, it was felt diffusely in the third, fourth and fifth interspaces in the region of the left nipple. Relative cardiac dulness extended in the first interspace 5.5 cm to the right and 4 cm to the left of the midsternal line, and the greatest transverse measurements was 10.5 cm to the right in the fifth interspace and 15.5 cm to the left in the sixth interspace. The outline was typically pvriform. The sounds were faint, there were no murmurs. The rhythm was regular, the rate 80 per minute, at the apex and wrist. Blood pressure was systolic 190, diastolic 120, with no evidence of alternation. On pressure on the right vagus, there was a slowing of ventricular and radial rates to from 42 to 44 beats a minute. There was a transitional period of irregular rhythm following vagus stimulation. The liver edge was 6 cm below the right costal margin, there was shifting dulness in the flanks. The fundi showed moderate sclerosis of the retinal arteries, in keeping with a definite though not marked peripheral sclerosis. There was no retinitis.

Laboratory Findings—These were hemoglobin, 70 per cent, white blood cells, 9,800, polymorphonuclear leukocytes, 80 per cent, Wassermann reaction, negative, urine, of high concentration, with a cloud of albumin, numerous granular casts, and white blood cells.

Electrocardiograms—These were taken on admission prior to the administration of digitalis. They showed normal sinus rhythm at a rate of 80 per minute, with prolongation of the auriculoventricular conduction time in Leads I and III to 0.44 second. In Lead II the rate was slower, 74 per minute, and the P-R interval equaled 0.22 second. The ventricular complexes showed a slight right predominance, and were remarkable for the small size of the waves, which indicated a poor functional state of the heart muscle, as did the flat T-waves. The second record, taken during pressure on the right vagus, showed a transitory period of 2 1 heart block, followed by varying grades of auriculoventricular dissociation. In Lead III, there were P-R intervals of 0.6 to 0.68 of a second.

Course—On February 24, three days after admission, because of failure to improve under rest and digitalis, 500 c.c. of pericardial liquid was withdrawn through a needle inserted close to the sternal border in the fifth left interspace.

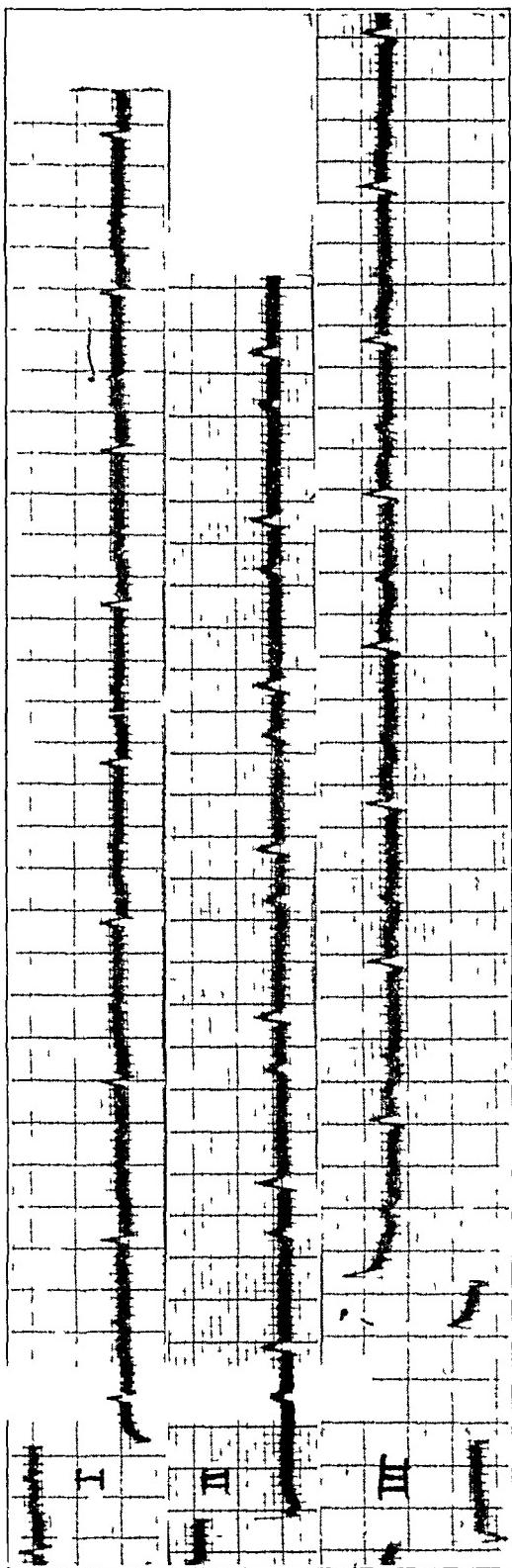


Fig. 1—E K G, Feb 21, 1921 $P-R$ interval 0.44 second in Leads I and III, 0.22 second in Lead II, amplitude of QRS group greatly diminished, T-waves flat

The tapping gave the patient immediate and great relief. The pericardial fluid had a specific gravity of 1.024, 12 gm of albumin per liter, and 6,690 white blood cells, 96 per cent lymphocytes, per cubic millimeter. Cultures and guinea-pig inoculation were sterile. On the day after paracentesis, a third electrocardiogram revealed a normal conduction time of 0.15 second, and a slight but definite increase in amplitude of the *QRS* group, as evidence of improved myocardial function.

After an uneventful convalescence, the patient was discharged on March 13 but three weeks later the heaviness in the abdomen and dyspnea returned, and the patient came back for a second tapping of 500 cc on May 5. On this occasion, the fluid contained 2,400 cells per cubic millimeter, almost entirely lymphocytes. Renal function tests at this time were within normal limits: urea nitrogen 9.2 mg, plasma chlorides 625 mg, and the phenolsulphonephthalein output 52 per cent in two hours. The specific gravity in two hourly urine specimens varied from 1.026 to 1.030. The electrocardiograms showed no change in conduction time during this readmission.

In December, 1921, after six months of freedom from symptoms, the oppression and the signs of effusion returned, and the patient was sent in from the cardiac clinic for a third paracentesis, which yielded 550 cc. On this occasion also the electrocardiogram recorded normal conduction time.

In the twenty months since the last tapping, there has been no evidence of return of fluid, and it is noteworthy that the series of electrocardiographic records shows a gradual increase in the size of the *QRS* group and a slight rise in the T-wave. On the whole, there has been a coincident improvement in the man's general condition and cardiac response.

ETIOLOGY OF HEART BLOCK

Reference to an authoritative text⁵ discloses that auriculoventricular heart block may be divided into three groups, according to the factors that give rise to the depression or failure of conduction over the bundle of His: (1) alterations in structure of the junctional tissues, (2) intoxications involving the bundle or its branches, (3) nervous influences, chiefly through the vagi, exerted on the conduction system.

The first group undoubtedly comprises by far the greatest number of cases of block, particularly the numerous examples of inflammatory and degenerative lesions incident to acute rheumatic⁶ and other infections. Gumma of the bundle is another well recognized cause of heart block.⁷ The instances of sclerosis of the junctional tissues are many, but here, it must be admitted, there is much lack of distinctness regarding both histology and functional pathology. We have in mind, as an example, a person with classical complete block and convulsive attacks, in whom the anatomic findings were minimal in respect to fibrosis or other changes in the junctional tissues. A series of similar instances of clear-cut clinical pictures without demonstrable anatomic bases has been

5 Cohn, A. E. Cardiac Irregularities, Nelson Loose-leaf Medicine New York 4 333E, 1920.

6 Christian, H. A. Med & Surg 1 911 1918.

7 Major, R. H. Stokes-Adams' Disease Due to Gumma of the Heart, Arch Int Med 31 857 (June) 1923.

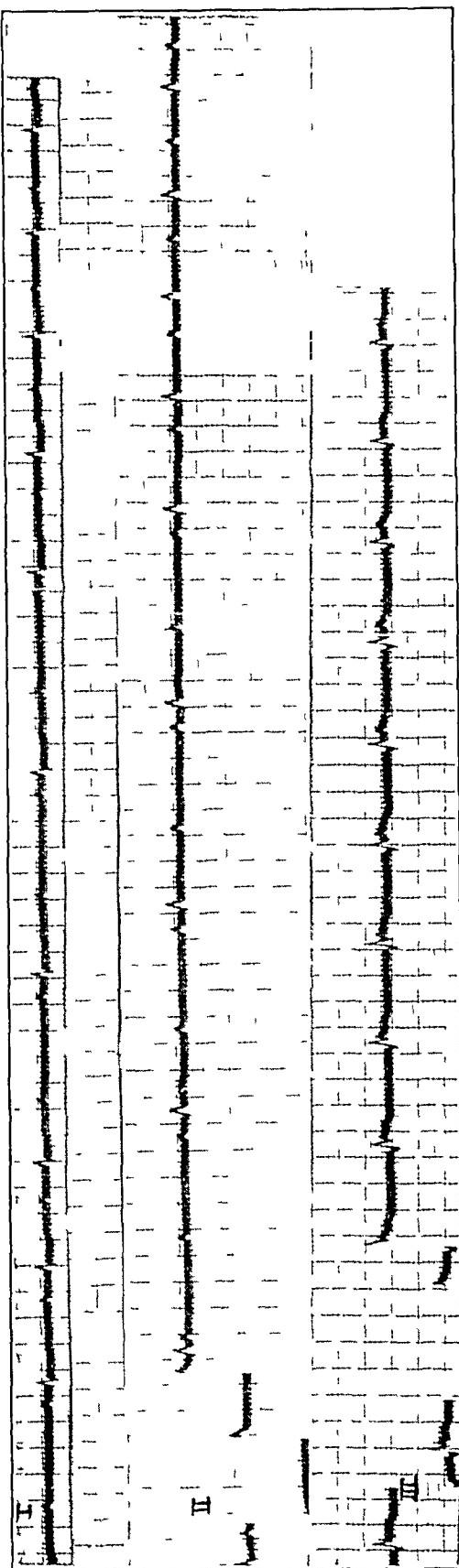


Fig. 2—E K G, Feb 21, 1921 2 1 heart block during right vagus stimulation, followed by varying degrees of auriculo-ventricular dissociation In Lead III, P-R interval equals 0.68 second

reported. Such observations, in the opinion of Krumbhaar,⁸ "tend to show that heart block, even when complete, may not only be temporary, but may depend on a much more complex condition than a simple lesion or destruction of the bundle of His."

Digitalis, of course, provides the greater number of cases in the second group, while a number of less commonly used drugs, diphtheria toxin and the products of intestinal toxemia and of asphyxia have been found involved in specific instances.

While various lesions along the course of the vagi, of which tumors of, or encroaching on, the vagal ganglions and diabetic neuritis involving the trunks are outstanding examples, have been reported as definite etiologic factors in heart block, it remains commonly true that it is unusual for vagal effect to be other than a relative bradycardia, except in hearts that are already damaged. This point of view is corroborated by the recent careful work of Kleemann.⁹

In this generally accepted etiologic classification of heart block which we have briefly reviewed, the case that we report is not easily included. Except for the remote possibility of tuberculosis, infectious factors appear to be eliminated, the impairment of conduction preceded administration of digitalis and was absent at the height of digitalis effect, after the first paracentesis, vagus stimulation was no longer effective, while the hypothesis of pressure on the nerve trunk by a distended pericardium or its contents, in a manner analogous to recurrent laryngeal nerve compression by auricular enlargement, dilatation or upward displacement of the pulmonary artery or aneurysm, seems beyond the bounds of anatomic possibility. What, then, was the cause of the lowered conductivity of the junctional system and the abnormal vagal effect accompanying this pericardial effusion?

The answer to this question, we believe, is to be found in the impaired blood supply to the bundle of His as a result of the direct interference with the intrinsic cardiac circulation by the pressure of the effusion on the coronary arteries and veins. To the decreased arterial in-flow and the increased venous congestion thus arising, must be added the embarrassment of coronary circulation due to the changes in intracardiac pressure relations which result from compression of the auricles.

Besides the deductions of Calvert already mentioned, drawn from pathologic evidence of compression, there is accumulating clinical data that have an important bearing on the point at issue of a circulatory

⁸ Krumbhaar, E. B. Adams-Stokes' Syndrome, with Complete Heart-Block, Without Destruction of the Bundle of His, *Arch Int Med* 5 583, (June) 1910

⁹ Kleemann, M. *Deutsch Arch f klin Med* 130 221 (Sept 26) 1919

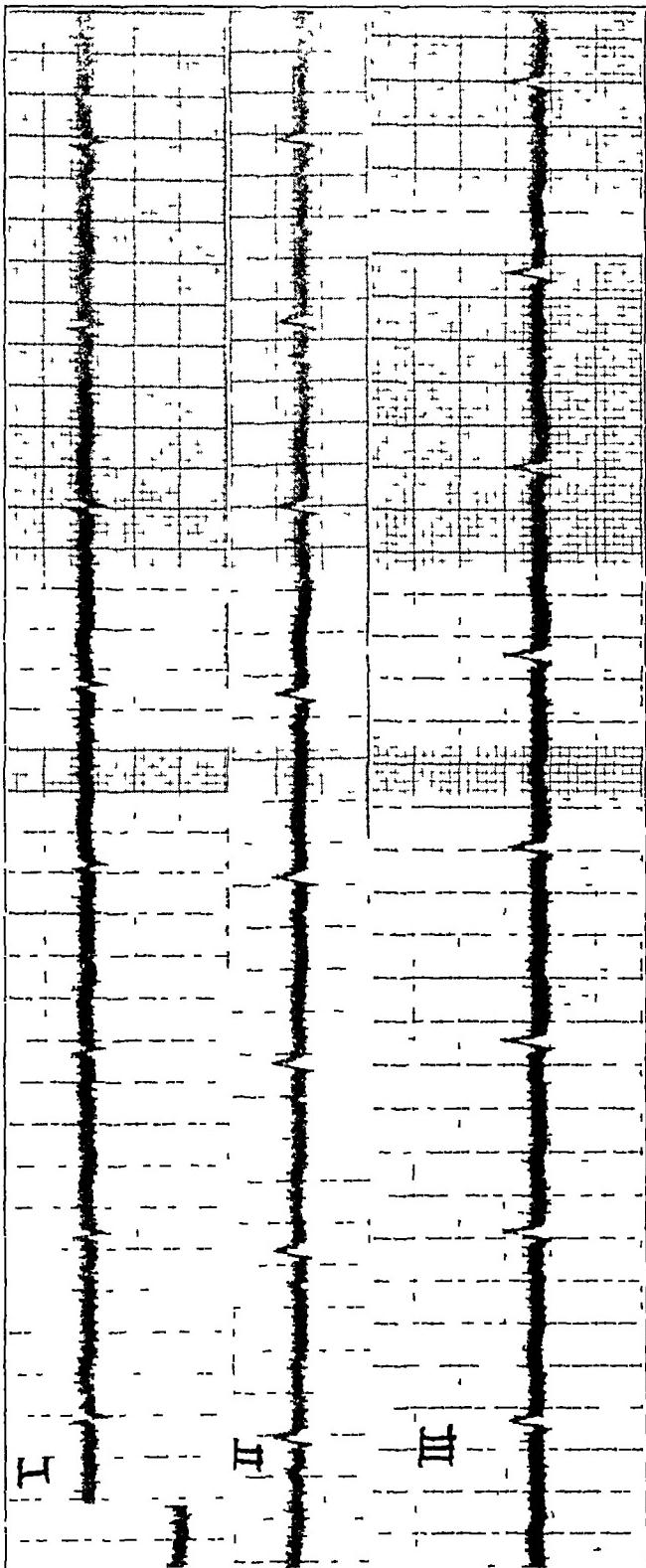


Fig 3—E K G, Feb 28, 1921 Following removal of 500 cc of pericardial liquid, P-R interval 0.15 second

factor in heart block Pardee¹⁰ has called attention to the occurrence of block of varying degree, usually only of delay in conduction, in patients with cardiac decompensation, and I have recently had an instance in the case of a woman aged 50, who came under observation complaining of shortness of breath on moderate exertion. The electrocardiogram showed a *P-R* interval of 0.22 second, a delay in conduction which has disappeared with restoration of cardiac sufficiency by rest. Herrick¹¹ has also commented on the disappearance of heart block under the improved circulatory conditions brought about by digitalis therapy. Twenty years ago, Wenckebach¹² wrote that the power of conduction was dependent in the first place on the presence of oxygen and Hirschfelder¹³ has suggested that ischemia may be sufficient to diminish conductivity.

A rather striking example of this circulatory factor in heart block is a case of complete dissociation accompanying auricular fibrillation recently reported by Neuhof¹⁴ in which there was the anatomic finding of complete calcification of that small branch of the coronary artery that supplied the auriculoventricular node. Although the sclerotic changes had been of many years' duration, and degeneration along the course of the auriculoventricular artery was present, the history and clinical evidence pointed to a sudden onset of the block, presumably due to final complete closure of this small vessel. Of doubtful import is Gerhardt's¹⁵ example of sclerosis of the artery supplying the *A-V* bundle, since cellular infiltration in the course of rheumatic fever was also present.

With such facts in mind, it seems not improbable that a certain number of cases of heart block, particularly among those of a functional¹⁶ or transient type, may fall into a circulatory group, with diminution or failure of the blood supply to the junctional tissues as the immediate etiologic factor. Such an ischemia or anemia of the conduction system would serve to explain certain of the clinical and electrocardiographic phenomena of block, as well as the paucity of anatomic findings in instances of definite clinical disease. For example, some

10 Pardee, H E B. The Relation of Heart-Block to Lesions of the Auriculoventricular Bundle, with Report of a Case, *Arch Int Med* **11** 641 (June) 1913

11 Herrick, W W. *Am J M Sc* **139** 246 (Feb) 1910

12 Wenckebach, K F. *Arrhythmia of the Heart*, trans., Snowball, Edinburgh and London, 1904

13 Hirschfelder, A D. *Diseases of the Heart and Aorta*, Ed 3, Philadelphia, J B Lippincott Co, 1918, p 579

14 Neuhof, S. *Am J M Sc* **165** 34 (Jan) 1923

15 Gerhardt, D. *Deutsch Arch f klin Med* **103** 485 (July 30) 1908

16 Hart, T S. *Am J M Sc* **149** 62 (Jan) 1915

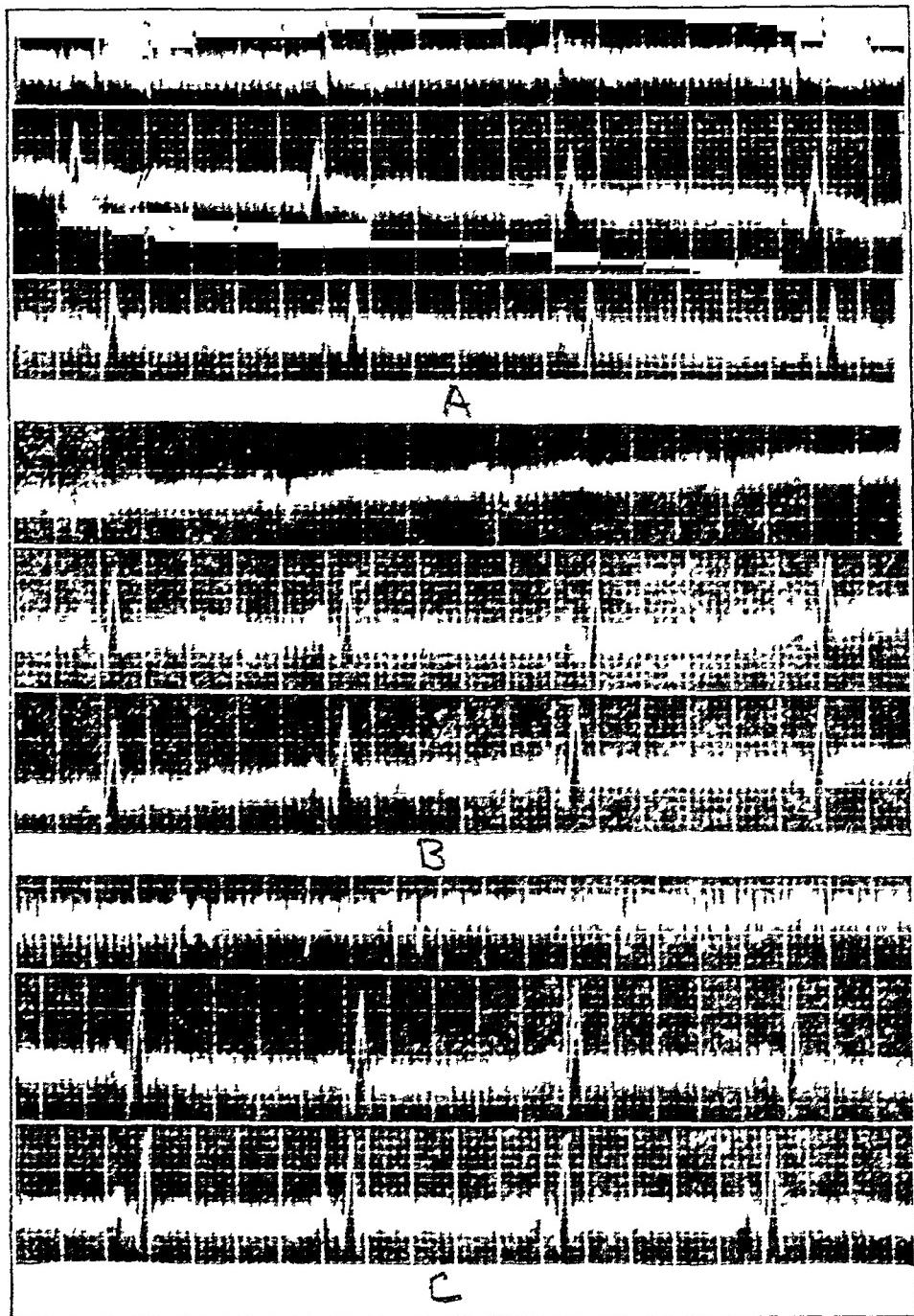


Fig 4—(A) E K. G., Dec 6, 1921, (B) Aug 17, 1922, (C) Nov 15, 1922
These records show increasing amplitude of the *QRS* group coincident with the patient's general progress, normal conduction time in all

of the instances of block associated with hypertension¹⁷ might readily fall within this clinical group. It would appear that attention directed toward the circulatory factor in heart block might aid in clearing up some of the present obscurity of its functional pathology. The necessary anatomic groundwork has recently been reviewed and added to by Gross¹⁸

SUMMARY

The occurrence of auriculoventricular heart block accompanying a large pericardial effusion is reported, with disappearance of the block following tapping.

The compressive effect of pericardial effusion on the heart is discussed, with particular reference to the embarrassment of intrinsic circulation through pressure on the coronary arteries and veins.

Impairment or failure of blood supply to the conduction system is pointed out as a possible cause of certain instances of heart block, especially those of transient or functional nature.

When the effects of infection, poisoning or nervous influences may be eliminated, the reasonableness of considering a local circulatory factor as a cause of block is suggested.

17 Musser, J. H., Jr. Heart Block Associated with High Blood Pressure, Arch Int Med 20:127 (July) 1917

18 Gross, L. The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, 1921

SYMPTOMATIC POLYCYTHEMIA WITH CYANOSIS AND DYSPNEA*

P F MORSE, M D

DETROIT

The purpose of this paper is to call attention to a group of cases showing the clinical signs of Ayerza's disease (sclerosis of the pulmonary artery) due to another pathologic condition and to offer some points which will aid in differentiating the various pathologic processes which may cause this syndrome.

Parkes Weber¹ classifies the pathologic conditions associated with "secondary" (symptomatic) forms of polycythemia rubra, and mentions the following classes of cases:

- 1 Polycythemia hypertonica, "Geisbocks disease"
- 2 Splenomegalic polycythemia rubra associated with tuberculosis of the spleen
- 3 Secondary polycythemia rubra with splenomegaly connected with a condition of visceral blood stasis of chronic thrombotic origin in the portal and splenic veins
- 4 "Cardiacos negros," "Ayerza's diseases," due to pulmonary sclerosis, pulmonary fibrosis, asthma, pulmonary emphysema, chronic bronchitis and pleural adhesions
- 5 Secondary polycythemia rubra connected with congenital or acquired heart disease

It will be seen that under Ayerza's disease, Parkes Weber groups all cases of erythrocytosis of pulmonary origin whether the pathologic process is primary in the pulmonary artery or elsewhere in the pulmonary or pleural tissues.

There is a distinct group of cases presenting the picture of extreme cyanosis, especially of the upper parts of the body, with marked injection of the conjunctivae, attacks of dyspnea of an asthmatic character, and profuse mucopurulent and bloody expectoration coupled with gradually developing erythremia. When we examine these cases for the common etiologic factors concerned with cyanosis and dyspnea, we find that the usual mechanical factors accompanying such a condition are lacking.

Valvular disease of the heart, collections of fluid in the serous cavities and mediastinal tumor are ruled out in turn. No outstanding physical signs are elicited to account for the patient's condition. The

* From the Diagnostic Clinic, Harper Hospital

1 Parkes, F. British M J 2 658 (Oct 30) 1920

history is usually as follows. A middle aged man gradually develops a cough with mucopurulent expectoration. The patient later notices that he becomes breathless on exertion and still later that definite attacks of dyspnea somewhat asthmatic in character become increasingly frequent, and cyanosis is gradually noticed developing as the attacks of dyspnea become more severe. The cyanosis gradually deepens and becomes especially prominent during the asthmatic attacks, but is still markedly noticeable in the interim. At this stage the patient usually seeks medical aid, and a physical examination is usually made during an attack while the patient is propped up in bed and is extremely dyspneic. The dyspnea is not the typical expiratory dyspnea of spasmodic asthma, but inspiration and expiration are equally labored, coupled with profuse mucopurulent sputum. The face is livid, the lips and ears are often almost black, and the conjunctivae are a deep red in sharp contrast to the blue lividity of the rest of the face. The patient appears extremely anxious, and the accessory respiratory muscles are all called into play. The chest is usually barrel shaped and emphysematous in type. The intercostal spaces show little retraction during inspiration, and the abdominal movements are of the normal type. Cyanosis of the lower extremities may be marked during attacks but is usually less marked than that of the head and neck. In cases uncomplicated by myocardial exhaustion, there is no edema of the feet and extremities, and no fluid can be detected in the abdomen. The apex beat may or may not be seen, and when noted is usually inside the nipple line and diffuse in character. On palpation no signs are elicited which give a clue to the condition of affairs. Tactile fremitus may be slightly decreased or definitely increased throughout. On palpation of the abdomen, the liver may sometimes be felt below the costal margin, occasionally the spleen is palpable, but more often not. An especial feature of the syndrome is the absence of striking splenic enlargement.

Percussion reveals a somewhat hyperresonant note such as is expected in emphysema. The area of cardiac dulness is not enlarged, and the right border of the heart is obscured by the hyperresonant anterior border of the right lung. In some cases an indefinite widening of the substernal dulness can be made out above the heart. Auscultation of the cardiac apex brings out a normal or practically normal first sound, and a normal relation between the first and second sound is noted at the base. During an asthmatic attack gallop-rhythm may be noted, and after a prolonged paroxysm an indefinite systolic murmur is often associated with the gallop-rhythm and heard throughout the paroxysm. In the intervals between the attacks of dyspnea, all cardiac signs are negative. The breath sounds are emphysematous in type with prolonged harsh expiration. Many râles of all types are heard during the asthmatic attacks, and the vibrations of coarse rhonchi may even be felt through

the chest wall. The sputum is copious, mucopurulent in character, richly blood streaked, or diffusely pink during the paroxysms and may have special features such as anthracotic phagocytes Curschmann's spirals, Charcot Leyden crystals, or eosinophilia such as are found in true asthma are lacking.

The outstanding feature of the laboratory findings is the polycythemia of moderate grade. The red count is 7,500,000 or over, and usually not below 6,500,000. Hemoglobin estimations range from 100

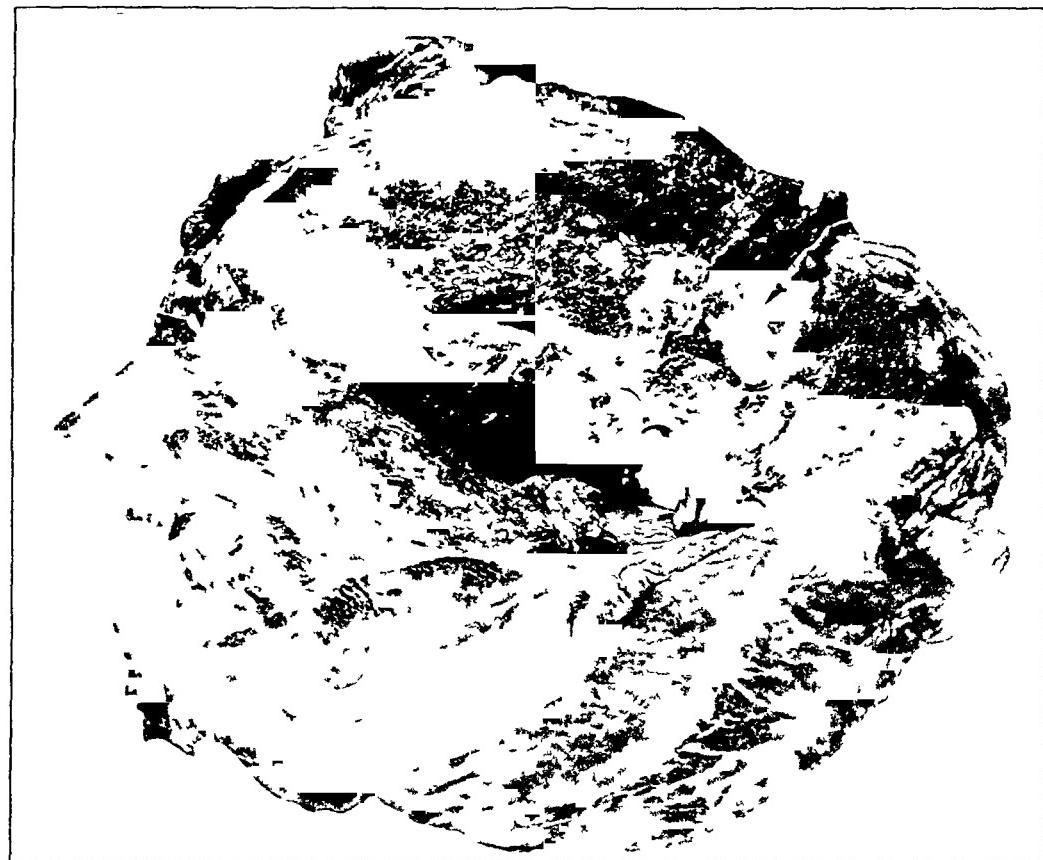


Fig. 1.—Extreme pulmonary anthracosis with cavitation

to 120 per cent. The leukocyte count is slightly elevated or normal with a normal percentage relation of the various white cells. The urine has no special features.

It will be noted that thus far we have evidence of a severe disturbance of aeration of the blood, cyanosis, dyspnea and polycythemia without the gross mechanical factors mentioned above to account for it. The difficulty must be sought in a disease of the external respiratory membranes themselves rather than in some gross mechanical factor—that is, in those tissues concerned in the interchange of gases between the outside air and the blood.

The pathology of one group of these cases was first recognized by Ayerza under the title "cardiacos negros" (Warthin²) and especially emphasized by Warthin² in America, by F Parkes Weber¹ in England and by Bezancón³ in France.

The following records are given to show that typical clinical signs of "cardiacos negros" or "Ayerza's disease" are not uncommonly found due to diffuse fibrosis and destruction of the pulmonary parenchyma from extreme anthracosis as in the case of coal miners or to chronic diffuse infection of unknown etiology.

REPORT OF CASES

CASE 1—*History*.—A man, aged 40, complained of cyanosis and dyspnea. The patient was admitted to the hospital in a wheel chair and was put to bed. He was of Polish extraction. He rested propped up in bed. His respirations were 20, pulse 96, temperature 98.8 F. There was marked cyanosis involving the entire body but most marked about the lips and ears. His breathing was regular, there was no particular distress. He said that he had no pain. He was at once sent out on the fresh air pavilion. Oxygen was given, and the cyanosis cleared up within a few minutes. He was talking rationally and said that he would be all right after resting a little while.

The patient said that he had had a similar sickness about one year before and had quickly recovered. He had gone back to work and had been working steadily ever since. A friend said that he had been drinking a good deal of "moonshine" whisky. The friend said that the patient had frequently been "fighting" drunk. His wife said that the patient had had a cough for the past eight years and that he had been raising blood for the past two years. He had been employed all his life as a coal miner or worker in coal yards. He had had several attacks of cyanosis. He had been mildly delirious at home. On several different occasions his clothes had been set on fire. He had been taken to the hospital in January with a condition of marked cyanosis, from which he had recovered. A diagnosis of polycythemia had been made. The blood cells numbered 7,500,000.

Physical Examination.—The patient was resting in bed. There was marked cyanosis of the lips, ears and hands. There was a lesser cyanosis covering the entire body. He was perfectly conscious and talked freely. His head, eyes, ears and nose were negative. His teeth were in poor condition. There was marked pyorrhea. There was a small ulcer on the mucous membrane of the lower lip where it touched the sharp edge of a tooth. There was a thick yellowish secretion in the mouth. The throat was reddened. There was no rigidity of the neck. The chest was poorly nourished, symmetrical in shape. Intercostal spaces were prominent. Respiration was equal on the two sides. Respiration was thoraco-abdominal in type. Tactile fremitus was normal throughout the entire chest. There was hyperresonance throughout. The breath sounds were roughened with a few râles found in the upper right anterior part of the chest. Coarse vibrating rhonchi were heard throughout. There was no cardiac impulse visible or palpable. The borders of the heart could not be made out. The heart sounds were distant. No distinct sound could be heard. The radials were equal, full and regular, with a rate of 96 per minute. There was no palpable tumor mass. There was some muscle rigidity of the abdomen,

² Warthin Contributions to Medical and Biological Research Dedicated to Sir William Osler, New York, Paul B Hoeber, 1919, p 1042

³ Bezancón, F La Presse Medicale, 28 885, 1920

but this was more voluntary than involuntary. Examination of the genitalia was negative, as were the neuromuscular and joint examinations.

Laboratory Findings.—The blood count revealed 6,920,000 red blood cells, 11,100 white blood cells, 79 per cent of polymorphonuclears and 21 per cent of mononuclears. Urinalysis revealed specific gravity, 1.008, acid, clear, straw color, free from sugar, trace of albumin. Throat culture showed staphylococcus and streptococcus. The throat smear was negative for Klebs Loeffler bacillus. There were many pus cells. Sputum examination was negative for tubercle bacilli. It showed free red blood. The blood Wassermann test was negative. There were 37.5 mg noncoagulable nitrogen per 100 cc of blood and 55.1 per cent by volume of carbon dioxide.

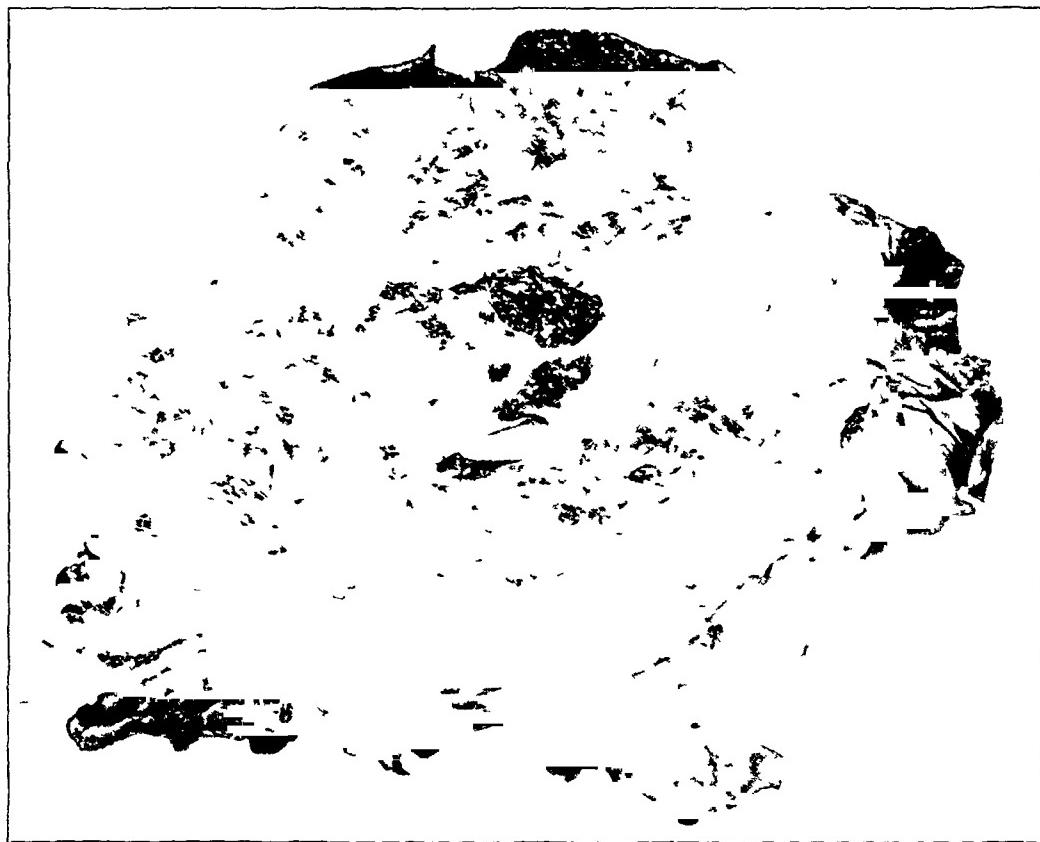


Fig 2.—Extreme pulmonary anthracosis with cavitation

Roentgen-Ray Report.—A fluoroscopic study was made of the chest. No definite deformity of the heart shadow could be demonstrated. The size of the shadow was within the normal limits. Definite accentuation of the root shadows was noted, also prominent linear markings and some diffuse parenchymal infiltration. The appearance of the fluoroscopic picture was not that of a circulatory pathologic condition.

Roentgenograms were made of the chest. There were extensive root shadows, with the deposit largely diffuse on the left side and in part calcified on the right. There were also some calcified masses in the lower part of the right lung and in the parenchyma adjacent to the left root. There were prominent linear markings as described in the fluoroscopic notes. The roentgenologist concluded that the findings were those of a chronic infection or changes incident to dust inhalation. The patient said he was a coal worker and this occupation could account for most of the lung changes.

Comment—It will be noted that this case differs from typical cases of sclerosis of the pulmonary artery in the absence of the peculiar changes in the cardiac roentgenographic shadows emphasized by Warthin.

CASE 2—History—A man, aged 48, a coal miner, entered the hospital on March 15, complaining of dyspnea, cough and pain in the chest. He had had this trouble for six months. The family history was negative. The patient had had pneumonia at 20 years of age; otherwise he had never been sick in bed until six months before, when he caught a bad cold, and he had coughed ever since. At that time he weighed 180 pounds (81.6 kg.) and was very well and strong, but since then he had gradually lost weight, until he was markedly emaciated and too weak to walk. He had drunk heavily until three years ago.

Physical Examination—The patient was a man of middle age, large of frame, but markedly emaciated. He was propped up in bed and was markedly dyspneic. There was general cyanosis, especially marked in the upper portion of the body, the lips and ears were deep blue-black, the conjunctivae were dark beefy red. He coughed almost continually and expectorated large quantities of purulent sputum colored with bright pink blood. The pupils reacted normally. The tongue was heavily coated, and the teeth were in very poor condition. The veins of the neck pulsated markedly, and the cervical glands were palpable.

The chest was of the emphysematous type, and there were numerous distended venules over its anterior aspect. Expansion was equal on the two sides. There was well marked tactile fremitus with a hyperresonant percussion note throughout. Moist and musical rales and coarse rhonchi were heard over all the lung areas, front and back. The heart could be outlined by percussion. No apex beat could be seen. Only a faint first sound was heard at the nipple. In the aortic and pulmonic areas the first and second sounds could be heard and were of normal quality. At the ensiform and 2 inches to the right of the sternum in the sixth interspace a long blowing systolic murmur was made out. The liver was felt to extend one hand's breadth below the right costal margin and was tender. The spleen was not felt. There was marked edema of both legs. (During the patient's stay in the hospital ascites and edema of the scrotum developed.)

Laboratory Findings—Blood count revealed hemoglobin, 95 per cent (?) (Talquist), leukocytes, 7,400, polymorphonuclears, 78 per cent, small lymphocytes, 16 per cent, large lymphocytes, 6 per cent, red cells 6,360,000. No abnormalities were noted in the stained smear. Blood pressure was systolic, 130, diastolic, 80. The urine contained a trace of albumin and an occasional granular cast. In the sputum were pus and "heart failure" cells. No tubercle bacilli, eosinophilia or spirals were found.

Roentgen-Ray Examination—Examination of the chest revealed extensive infiltration of both lungs below the clavicle, a wide mediastinal shadow and rotation of the heart shadow. The roentgenograms suggested advanced tuberculous infiltration of the lungs and aortitis.

Because of the dense shadow at the base of the heart a clinical diagnosis of mediastinal tumor had been made. The patient died on May 3 with signs of cardiac failure.

Necropsy—The body was that of a man past middle age, and poorly nourished. General anasarca was present, especially of the lower limbs. There was bluish discoloration on the inner side of the right leg. The chest was barrel shaped. Petechial spots covered the thorax. There was marked cyanosis of the face and neck.

On section it was found that a clear amber ascitic fluid filled the entire abdominal cavity. The peritoneum was normal, the panniculus was scanty. The muscles were pale and watery.

The dome of the diaphragm was in the fourth interspace on the right and the fifth on the left

The liver was four fingerbreadths below the ribs in the parasternal line
Superficial inspection of the abdomen was negative

The right pleural cavity contained no fluid The left pleural cavity was full of dark amber fluid There were old adhesions on the left lung which was retracted from the chest There were old adhesions at the base The pericardium was adherent to the sternum in front

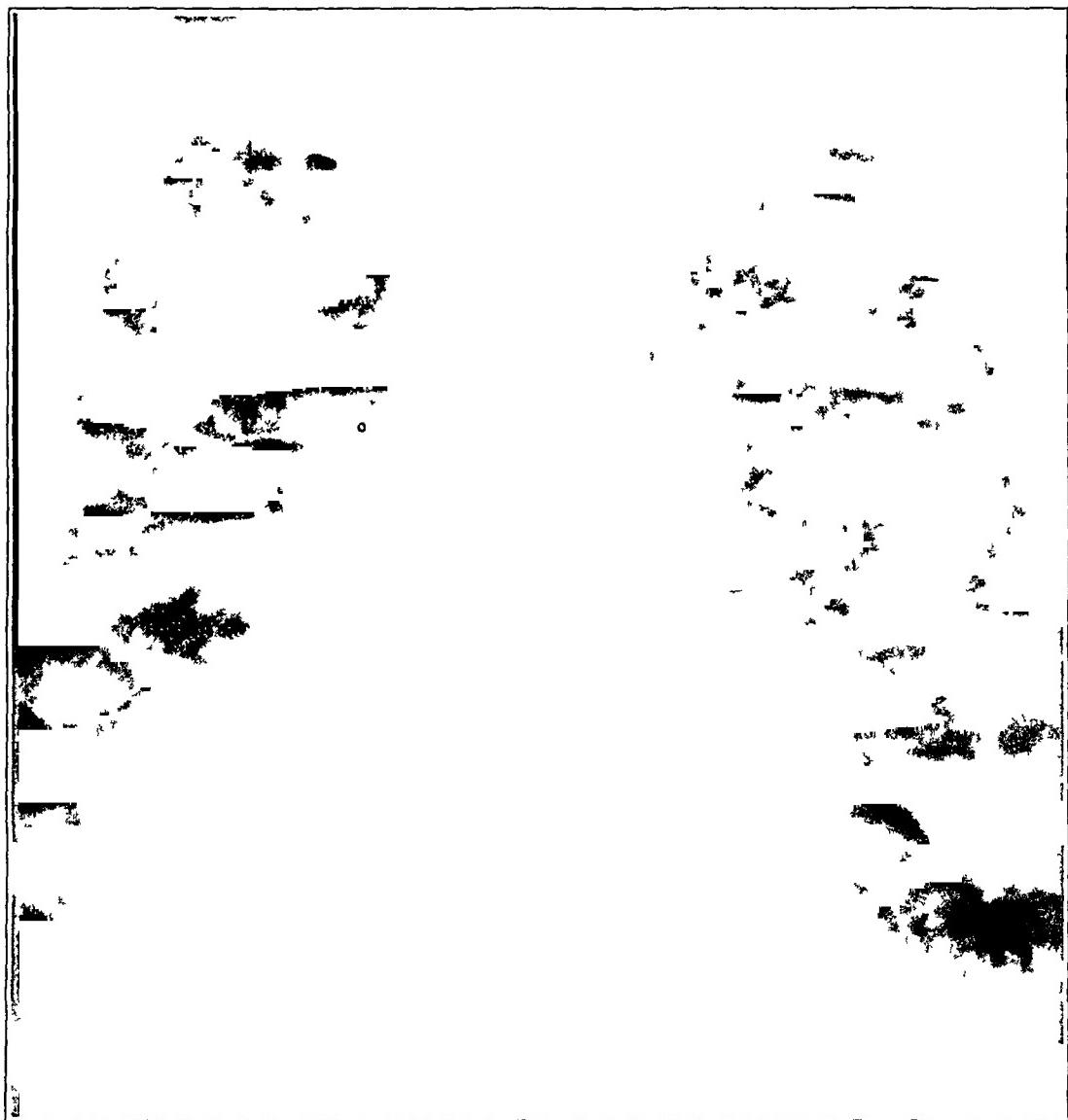


Fig 3.—Cardiac dilatation and pulmonary fibrosis in a patient with a positive Wassermann reaction

The apex of the heart was the fifth rib outside of the nipple line The pericardium contained 200 c.c. of clear amber fluid

The right lung adhered to the base behind by old adhesions The heart was dilated The right ventricle had chicken fat clot extending into the pulmonary artery The tricuspid ring was dilated, the tricuspid valves were negative The right auricle was empty The ear of the auricle had a small postmortem clot, the left ventricle had a small amount of postmortem clot

The mitral valve admitted two fingers with ease. A small postmortem clot was tangled in the mitral flap. The first part of the aorta showed linear sclerosis. The muscle of the left ventricle was normal.

The right lung was voluminous. The pulmonary vessels were dilated and thin walled, but no other gross lesion of the pulmonary artery was noted.

Both lungs were slate-like in color (Figs 1 and 2) and were uniformly gritty on cut section. When handled, coal black rubbed off on the prosector's fingers. There were numerous cavities from 1 to 5 cm in diameter in both upper lobes formed by the breaking down of atrophic alveolar septums. There was a mucopurulent discharge streaked with black in all the bronchi. The mediastinal lymph nodes were large and jet black, but no tubercles were discovered in them. The lung was full of small hard black nodules throughout. The pulmonary artery was empty. The left lung was covered with fibrinous exudate under which were areas of yellow thickened pleura. Large cavities in the left lung were hollowed out by breaking down the anthracotic lung tissue. There was no lesion of the pulmonary artery.

The spleen was smaller than normal. The capsule was thickened. There was diffuse darkening of the pulp. Malpighian bodies were not visible.

The left suprarenal was larger than normal. On section the medulla was found to be prominent. The left kidney showed depression of the upper pole. The cut surface appeared congested. There were no gross changes of importance. The right kidney was normal in size. On section it appeared to be congested. The right suprarenal also was larger than normal.

The liver was smaller than normal. There was a whitish scar on or near the right edge. Fatty change and congestion were found on section, there was no increase in the connective tissue.

The pelvis was normal.

The appendix was retrocecal, bound down by adhesions.

Diagnosis Anthracosis of the lung and cavitation, emphysema, cardiac dilatation.

Comment—This case resembled Ayerza's disease clinically more than the first one, because of the broadening of the base of the cardiac shadow. The significant features are the history of coal mining and the roentgen-ray evidence of pulmonary fibrosis. The aortitis and tuberculosis suggested by the roentgen ray were not confirmed by postmortem examination. The pathologic condition was such, however, as to make it indistinguishable from tuberculosis roentgenologically. The cavitation due to breaking down of coal dust laden septums in the lung parenchyma was striking. Here again we have the syndrome of cyanosis, dyspnea and polycythemia with chest findings indistinguishable from true Ayerza's disease but due to extensive anthracosis.

CASE 3—History—A man, aged 42, a laborer, entered the hospital on account of dyspnea, cyanosis, cough and expectoration. His past history was characterized by frequent and repeated acute infections, including scarlet fever, smallpox, measles, whooping cough and malaria. He had been in the hospital for two weeks two years ago for "kidney trouble." He had had "asthma" for ten or twelve years, associated with "kidney trouble," and he had had gonorrhea twenty years ago. His social and marital histories were negative. He had five children alive and well. His family history was negative. Six weeks before entering the hospital his asthma became worse and marked cyanosis and swelling of the extremities was noticed. He began to expectorate large quantities of blood tinged sputum.

Physical Examination—The patient was propped up in bed and markedly dyspneic and cyanotic His face and neck were especially cyanotic, and the conjunctivae were a dark beefy red The pupillary reactions and ocular movements were normal The ears and nose were normal The tongue was coated, and the teeth were in a bad condition with numerous cavities and extensive pyorrhea No pulsations were noted in the neck

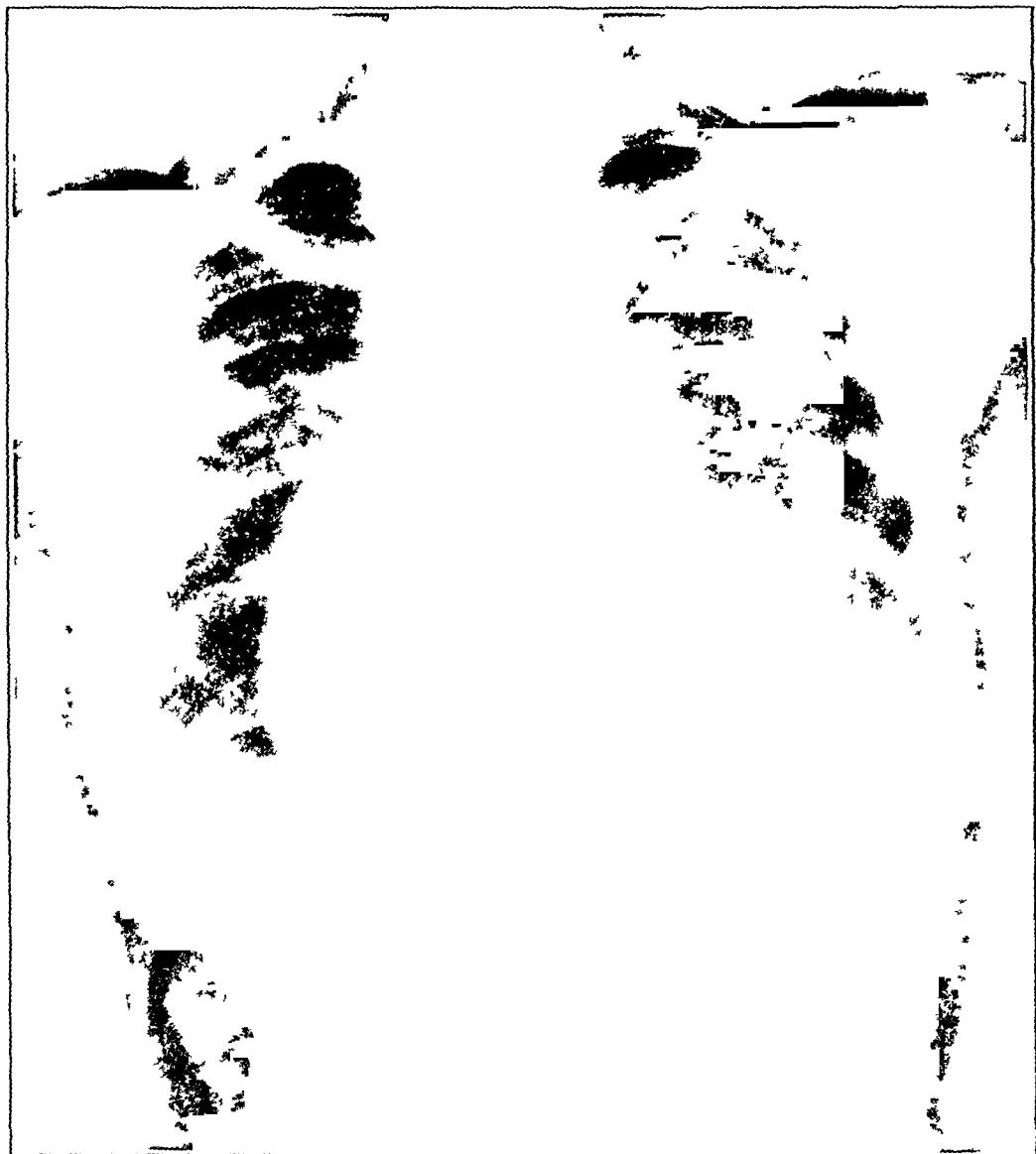


Fig 4 (Case 4)—Early stage of pulmonary fibrosis

The chest was barrel shaped and emphysematous Respiratory excursion was increased and the accessory muscles of respiration brought into play The apex beat was not seen On percussion the cardiac borders were not accurately made out because of hyperresonant lung sounds Auscultation revealed heart sounds of normal quality and rhythm, and many musical râles and coarse rhonchi were heard throughout the chest The abdomen was negative to the usual methods of physical examination There was marked edema of the feet Neuromuscular and joint examination was negative

Laboratory Findings—Urinalysis revealed a trace of albumin with a few granular casts. The blood count revealed red cells 7,700,000, white cells, 7,600, polymorphonuclears, 80 per cent, small mononuclears, 16 per cent, large mononuclears, 4 per cent, hemoglobin, 100 per cent. The smear showed an occasional nucleated red cell.

Röntgenologic Report—The chest findings were. The heart was considerably enlarged through the ventricles, especially the left. There was marked density shown at the hilum of the lung on both sides. The aortic shadow was not widened. The shadow of the hilum was considerably enlarged on the right, and there was diffuse fibrosis of both lungs. The blood Wassermann test was positive.

Treatment and Course—During the next week the patient exhibited no change of condition except marked lethargy and somnolence. The man was given vigorous mixed treatment and left the hospital slightly improved. He then disappeared from observation.

Comment—It is evident from examination of Figure 4 that the major pathologic rôle in this case was probably played by the heart. The amount of pulmonary fibrosis, while marked enough to be mentioned by the roentgenologist, was not thought to be as important as the cardiac finding.

This is an example of a case in which the diagnosis is in doubt as regards the nature of the underlying lesion. The positive Wassermann test along with the long history of "asthma" is suggestive of a syphilitic basis for the cardiac injury, but a lesion of the pulmonary artery could not be proved.

CASE 4—History—A woman, aged 32, married, entered the hospital on account of dyspnea and cyanosis which had been present for the past three months. The family and marital histories were negative. She had had the usual childhood diseases and pneumonia at 11 years of age, with good recovery. She had had no other illnesses. She had never had a sore throat. For some months past, the patient had noticed gradually increasing breathlessness on exertion. She had passed through two normal pregnancies. She had had acute appendicitis early in her second pregnancy and had been operated on, with good recovery.

Physical Examination—A fairly well nourished young woman was lying in bed. There was marked pallor of the skin, but the lips, face and extremities showed marked cyanosis. The venules over the anterior thorax were prominent. The breathing was rapid and deep as though the patient had recently been running, but no respiratory obstruction appeared to be present. There was a slight cough and a moderate amount of sputum. The apex beat was seen in the fifth interspace within the nipple line. The heart rate was 104 and the respiration 34. Percussion revealed cardiac dulness extending to the nipple line and normal resonance throughout the chest. Auscultation revealed rapid heart sounds, abnormal in quality. No murmurs were heard. The breath sounds were rather harsh but vesicular in quality, and no areas of consolidation were made out. There were a few dry rales at the apices. The abdomen and extremities were negative. Neuromuscular and joint examination was negative. Laryngeal examination was negative. The tonsils were enlarged with cheesy detritus in crypts. Sputum examination revealed a few leukocytes and streptococci. The patient did not have a rise in temperature while in the hospital.

Laboratory Findings—Blood examination revealed red blood cells, 5,920,000, white cells, 14,700, polymorphonuclears, 78 per cent, small mononuclears, 10

per cent, large mononuclears, 11 per cent, eosinophils, 1 per cent. The blood Wassermann test was repeatedly negative. Urinalysis was negative.

Roentgenologic Examination.—Examination of the chest gave rise to some controversy. One roentgenologist interpreted the findings as indicating mediastinal tumor, two others held that the picture was that of pulmonary fibrosis of nontuberculous character, and the medical director of a large sanatorium for

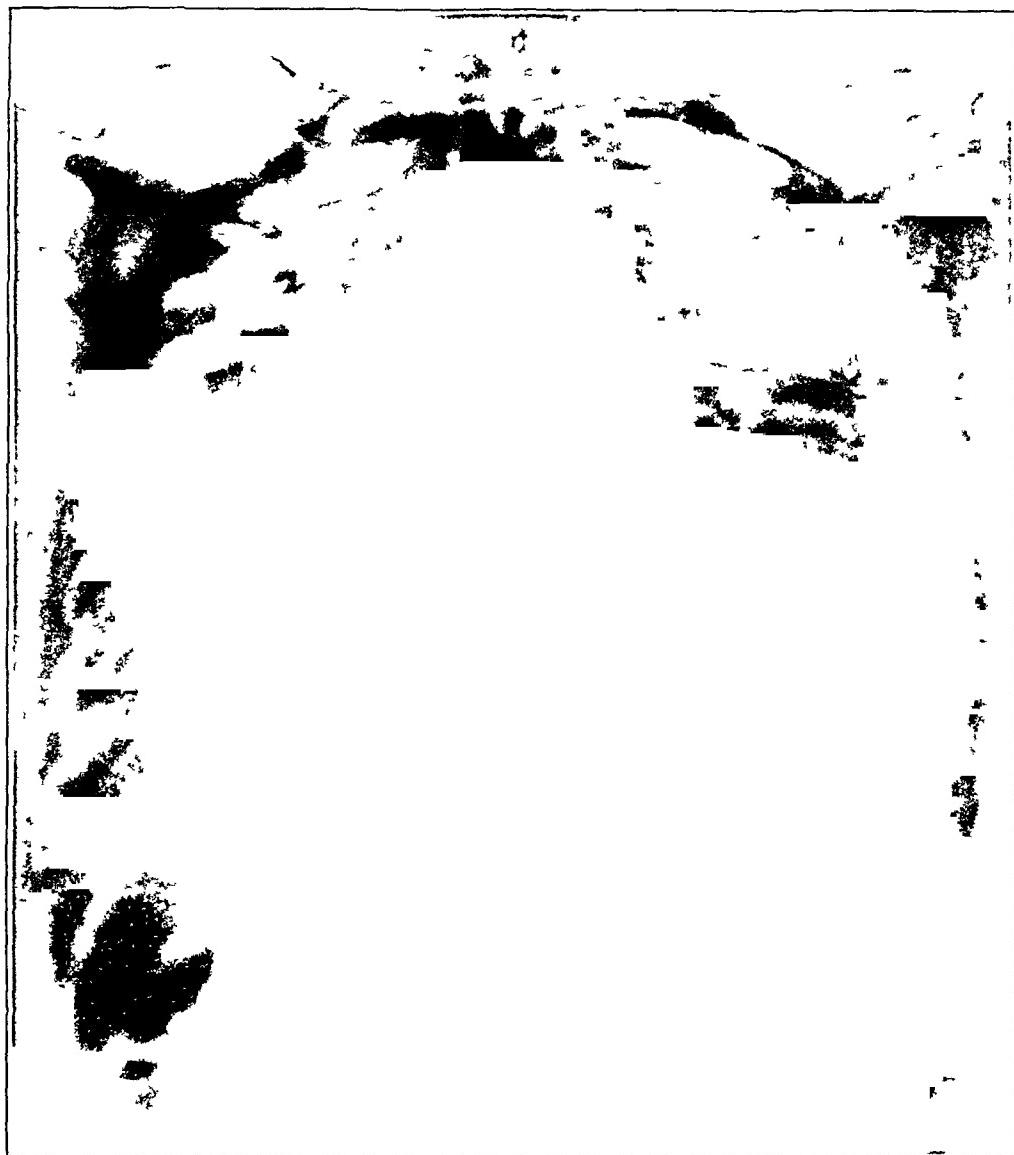


Fig. 5 (Case 4).—Late stage of pulmonary fibrosis.

the care of tuberculous patients, after seeing several films of the chest and examining the patient repeatedly, said that in his opinion the condition was tuberculous.

A large number of chest films were made over a period of two years and showed all stages from diffuse fibrosis of moderate grade to intense opacity at the mediastinum and bases, so that just before death the diagnosis of neoplasm seemed more probable, although the roentgenologists who took the plates insisted that the condition was not neoplastic but inflammatory in nature (Figs. 4 and 5).

Diagnosis Several clinical diagnoses were made by various consultants, among them pulmonary tuberculosis, mediastinal tumor, lymphosarcoma of the bronchial glands and diffuse pulmonary fibrosis due to infection of unknown origin. The outstanding features were as noted, dyspnea, cyanosis and polycythemia without evident gross intrathoracic pathology to account for the syndrome until the roentgen-ray findings shortly before death revealed the marked pulmonary fibrosis.

Necropsy—The body was that of a fairly well nourished woman about 20 years of age. The skin was pale, with marked cyanosis of the lips and finger tips. There were no external markings of importance. Necropsy permission was limited to examination of the thorax. On opening the thorax we found the thymus persistent but not enlarged and extending down to the ear of the right auricle. The pericardium was normal. The tissues of the anterior mediastinum were thickened and contained lymph nodes which were somewhat enlarged and on section showed definite inflammatory reaction. No tubercles or neoplastic process was found. The heart was definitely hypertrophied. There was well marked sclerosis of the first portion of the aorta and definite sclerosis of the first portion of the pulmonary artery. The sclerosis was nonspecific in type. Both lungs were uniformly hard and on removal were found to be small and dense. They were uniform externally and presented no nodules or localized areas of infiltration. The condition of the whole lung resembled that of a diffuse unresolved pneumonia. There was uniform increase of the connective tissue extending out from the bronchial tree to the cortex. No tuberculous process was present.

Microscopic examination showed diffuse round cell infiltration of the lung parenchyma accompanied by a uniform productive pneumonitis.

Diagnosis Chronic infectious pneumonitis, chronic mediastinitis, pulmonary fibrosis, secondary symptomatic polycythemia.

Comment—The point of entry of the infection in this case is unknown, but it is assumed to be the tonsils since they were reported grossly pathologic by the laryngologist. The case differs from the others in several particulars. There was no orthopnea even when the dyspnea was at its worst. The breathing was of a peculiar rapid quality resembling that of a runner rather than labored and difficult as is usual in these cases. The cyanosis was confined to the lips and finger tips, and the face was not suffused or the conjunctivae injected. The white count showed a distinct reaction to infection in spite of absence of fever, although this phenomenon might well have been considered, and was indeed so interpreted by one consultant, as being due to neoplastic extension with breaking down of the immune processes against malignancy.

The microscopic picture was that of active diffuse pneumonitis with extensive round cell infiltration and thickening of the alveolar septums due to proliferation of young fibroblasts. There was distinct alveolar catarrh, with desquamation and proliferation of the alveolar epithelium. There was no lesion of the branches of the pulmonary artery (Figs 6 and 7).

COMMENT

It is evident that the syndrome described above depends on the pulmonary fibrosis caused in two cases by coal dust and in the third and fourth by irritation and infection of unknown origin. In none of them were the lesions of the pulmonary artery significant. In a fifth case there was extensive pulmonary arterial syphilis unaccompanied by the Ayerza syndrome because of the absence of the necessary degree of pulmonary fibrosis. This case was one of aortic aneurysm in which

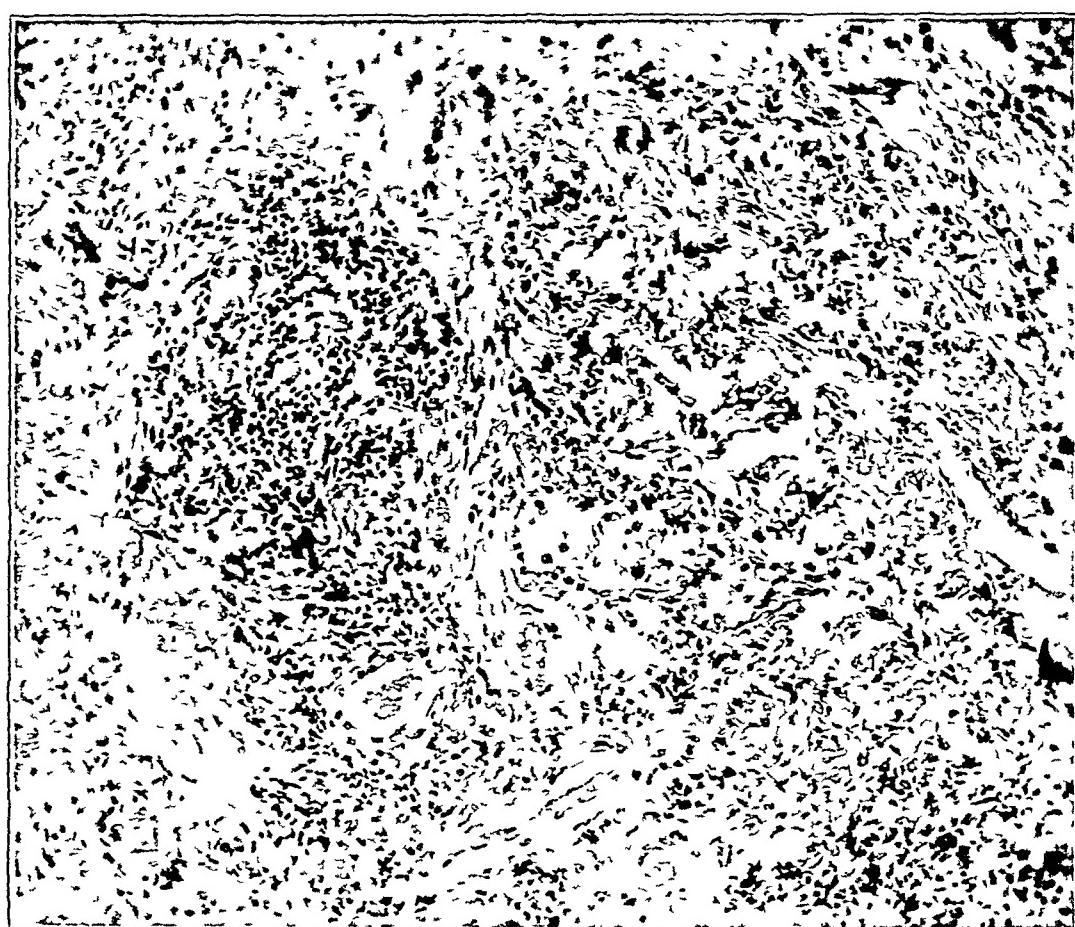


Fig. 6 (Case 4) —Diffuse pneumonitis with fibrosis

death was due to rupture into the pleural cavity. At the postmortem examination, extensive syphilis of the pulmonary artery was found besides the lesion in the aorta. The condition was relatively active and recent with patchy areas of fibrosis in the lung interspersed with large amounts of relatively normal lung parenchyma. The case history and physical findings are not given in detail because the case did not resemble the other ones in any way clinically. There was no cyanosis and dyspnea, and a moderate anemia was present instead of an erythremia.

The development of the polycythemia in the first four cases is easily understood and was a prominent feature of all of them Legge⁴ has recently reported that the syndrome caused by inhalation of quartz dust by gold miners is unaccompanied by polycythemia but is especially characterized by marked anemia Apparently the anemia must be explained by other factors at work in these cases besides the pulmonary irritation, because the pulmonary pathology per se would tend to produce the opposite effect Pulmonary fibrosis in general due to whatever cause tends to produce erythrocytosis, unless other factors prevent its development

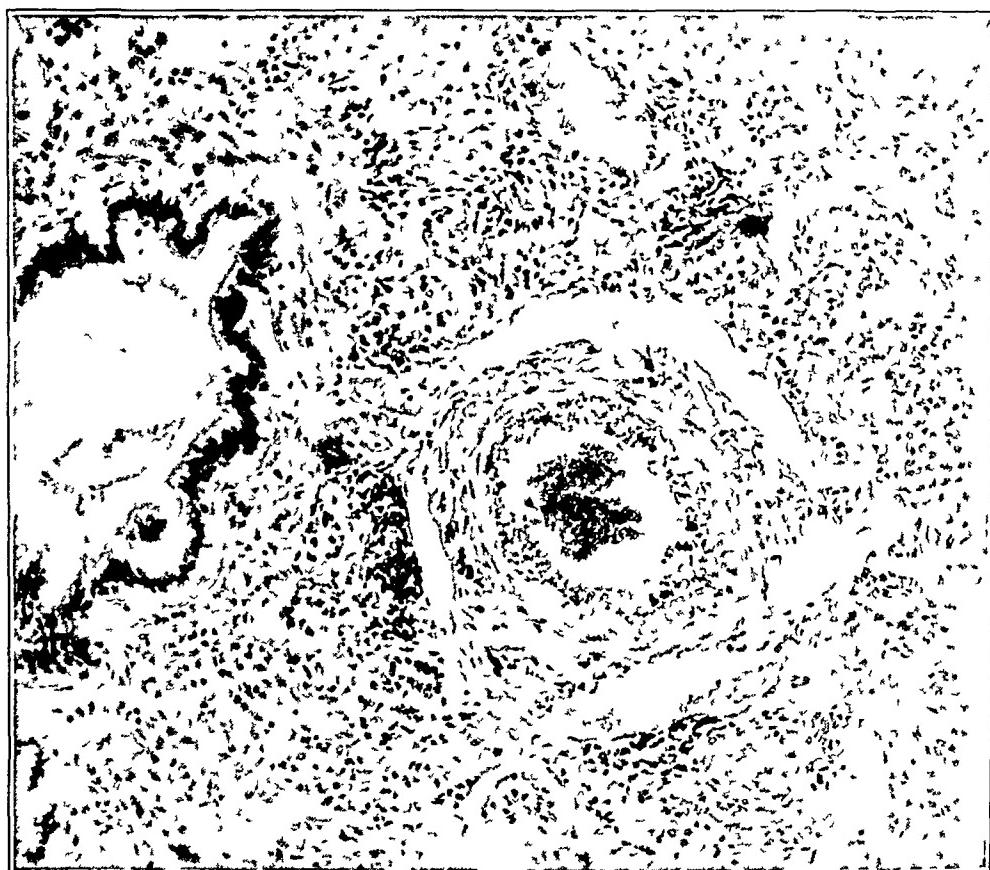


Fig 7 (Case 4) —Diffuse pneumonitis with fibrosis and alveolar catarrh

SUMMARY

Five cases are reported, four of which present clinical features closely resembling Ayerza's syndrome but due to pulmonary fibrosis rather than primary disease of the pulmonary artery The fifth case illustrates the fact that extensive pulmonary arterial syphilis may occur without Ayerza's syndrome

⁴ Legge, Robert T Miners Silicosis, J A M A 81 809 (Sept 8) 1923

DIRECT BLOOD-STREAM INFECTION THROUGH THE TONSILS*

S J CROWE MD

BALTIMORE

"Do the tonsils show any peculiar anatomical structure or possess any specific physiology or undergo pathologic changes that would make them more liable to act as a gateway of infection than other structures in the body?"¹ The histologic factors in chronic tonsillitis are (1) loss of epithelium on the surface or in the crypts, (2) the presence of masses of keratinized epithelial cells in the crypts, (3) hyperplasia of endothelial cells (4) accumulation of plasma cells lymphocytes and leukocytes around the margin of the crypts, (5) evidence of hemorrhage in the parenchyma or in the lumen of the crypt, (6) the presence of polymorphonuclear cells and lymphocytes in the epithelium lining the crypts, (7) the presence of bacteria in the crypt epithelium and in the parenchyma of the tonsil (probably in lymph channels or blood vessels), (8) thickening of the capsule and increased fibrosis of the trabeculae. In every case of acute tonsillitis and in a majority of those with a chronic tonsillitis the lymph glands of the deep cervical group near the angle of the jaw are palpably or visibly enlarged, and suggest that the portal of entry is through the lymphatics.

In a previous publication,² in 1916, I insisted that the tonsils or adenoids could not be responsible for a general systemic disturbance, such as infectious arthritis, unless there was a palpable enlargement of the lymph glands in the neck, and for many years such patients were advised that there was no indication for an operative removal of their tonsils or adenoids. Many of these patients, however, subsequently informed me that after leaving the Johns Hopkins Hospital they consulted another physician who advised a tonsillectomy, and that soon after the operation their symptoms began to improve and ultimately they were cured. This stimulated us again to study histologically our collection of tonsils and adenoids (removed from 3 000 patients during the

* From the Department of Surgery of the Johns Hopkins University and Hospital

* Presented before the Medical Society of the Johns Hopkins Hospital in November, 1923

1 Wood, G B Dangers of Tonsillectomy, Am J M Sc **154** 88 (Aug 1917)

2 Crowe Watkins and Rothholz Relation of Tonsillar and Nasopharyngeal Infections to General Systemic Disorders, Bull Johns Hopkins Hosp **28** 1-63 (Jan) 1917

past ten years) in order to see whether we could demonstrate a direct infection of the vascular system.

Our first encouraging finding was the fact that the epithelium on the surface and the epithelium lining the crypt differ markedly in their

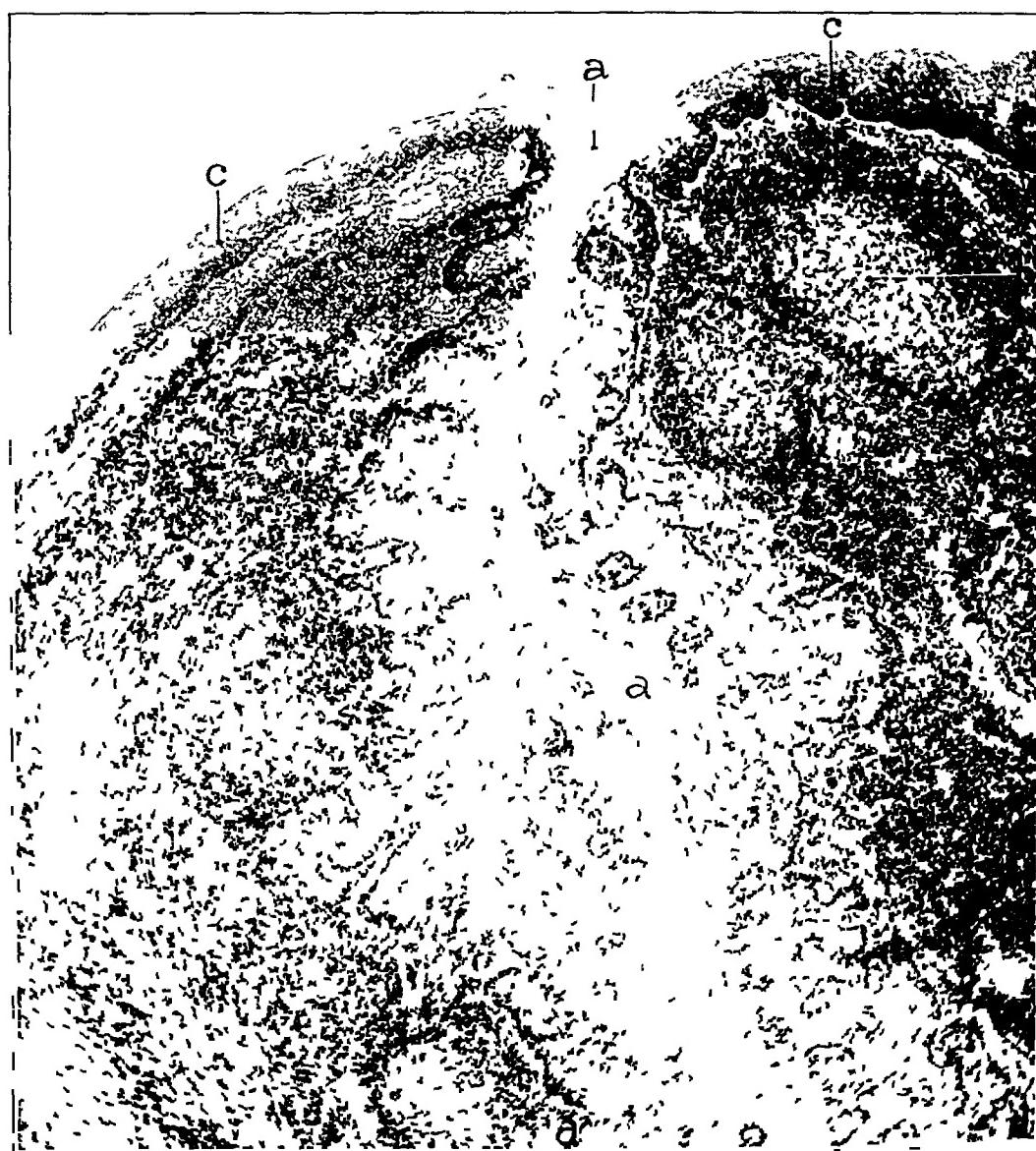


Fig 1.—Section of a normal tonsil, showing the difference between the epithelium on the surface and that lining a crypt *a*, lumen of crypt, *b*, lymph follicle, *c*, epithelium on oral surface, *d*, epithelium lining a crypt. The rich blood supply of the crypt epithelium may be noted.

blood supply. Figure 1 shows the appearance of a normal crypt. The epithelium here has papillae similar to those in the skin, and, like the skin, is rich in capillaries. A complete absence of or a marked hyalinization of the epithelium lining the crypts is the most common finding in

tonsils removed at operation. It is uncommon to find any changes in the epithelium on the surface of the tonsil (Fig. 2). This suggests that the destruction or localized ulceration of the epithelium in a crypt (as shown in the remaining illustrations) is associated with a thrombosis of the blood vessels that are normally present in this epithelium.

These findings suggest that the general systemic disturbances associated with a chronic tonsillitis or a chronic nasopharyngitis may be due

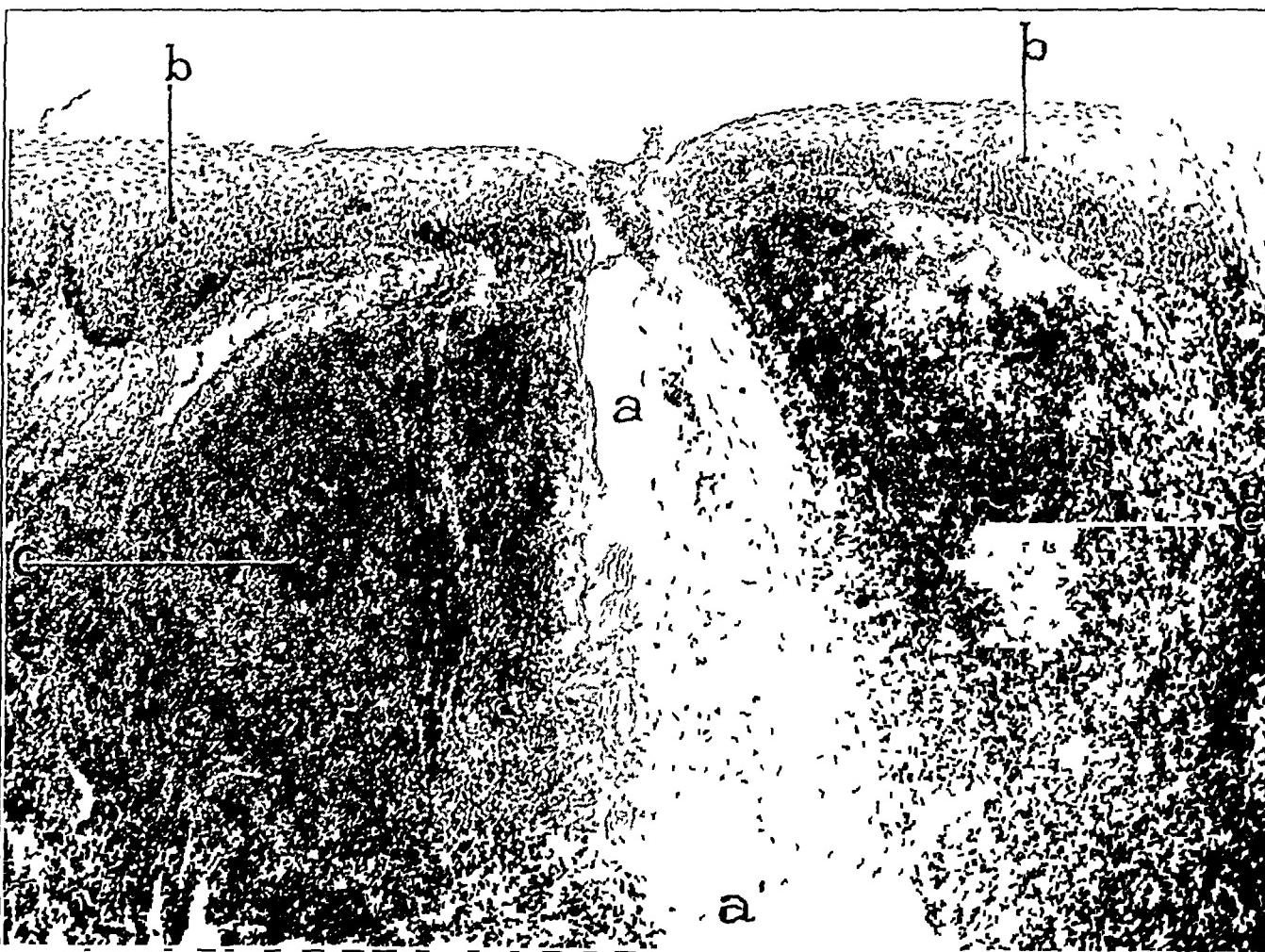


Fig. 2.—Section of a chronically infected tonsil. *a*, *a'*, lumen of crypt partially filled with cellular debris and inflammatory cells. The complete destruction of the epithelial lining of the crypt may be noted; *b*, epithelium on the oral surface, thickened but otherwise normal; *c*, accumulation of plasma cells, lymphocytes and leukocytes around crypt.

to direct blood-stream infection. The destruction of the epithelium lining the crypt may be acute and widespread, and if there is good drainage from the crypt into the oral cavity the ulcerated area may heal rapidly. If an ulceration of the epithelium occurs in a crypt in which there is a stricture at the orifice, the resulting accumulation of cellular debris and bacteria prevent healing, and a chronic ulcer results, with

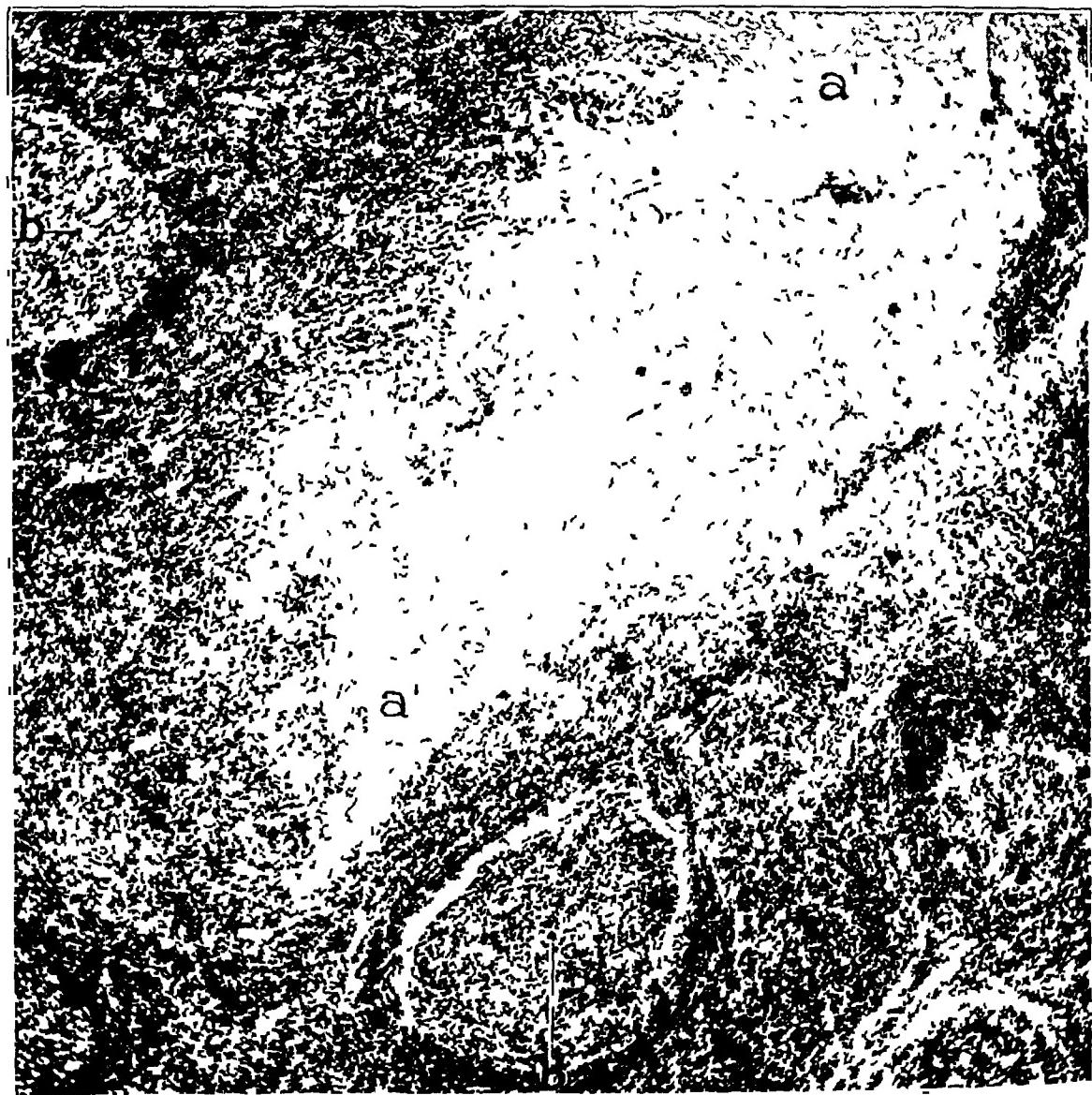


Fig 3.—The bottom of the crypt shown in Figure 2 *a*, lumen of crypt filled with debris, *b*, germinal centers. The absence of the lining epithelium may be noted.

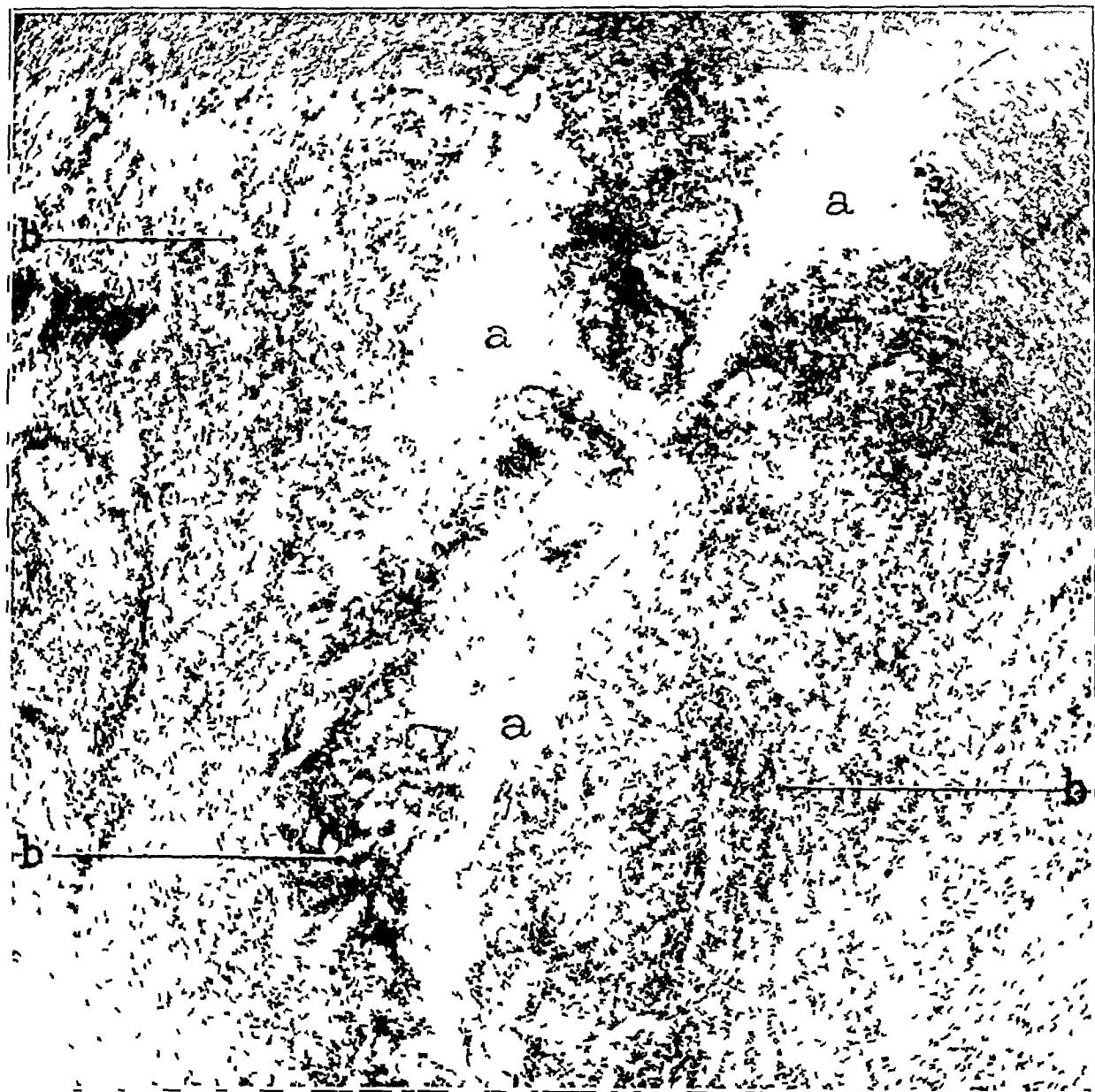


Fig 4.—A common finding in chronic tonsillitis *a*, lumen of a crypt. The absence of lining epithelium may be noted. A rich network of capillaries surround the crypt on all sides. Under a higher magnification, red blood cells are seen in each of the areas indicated by *b*.

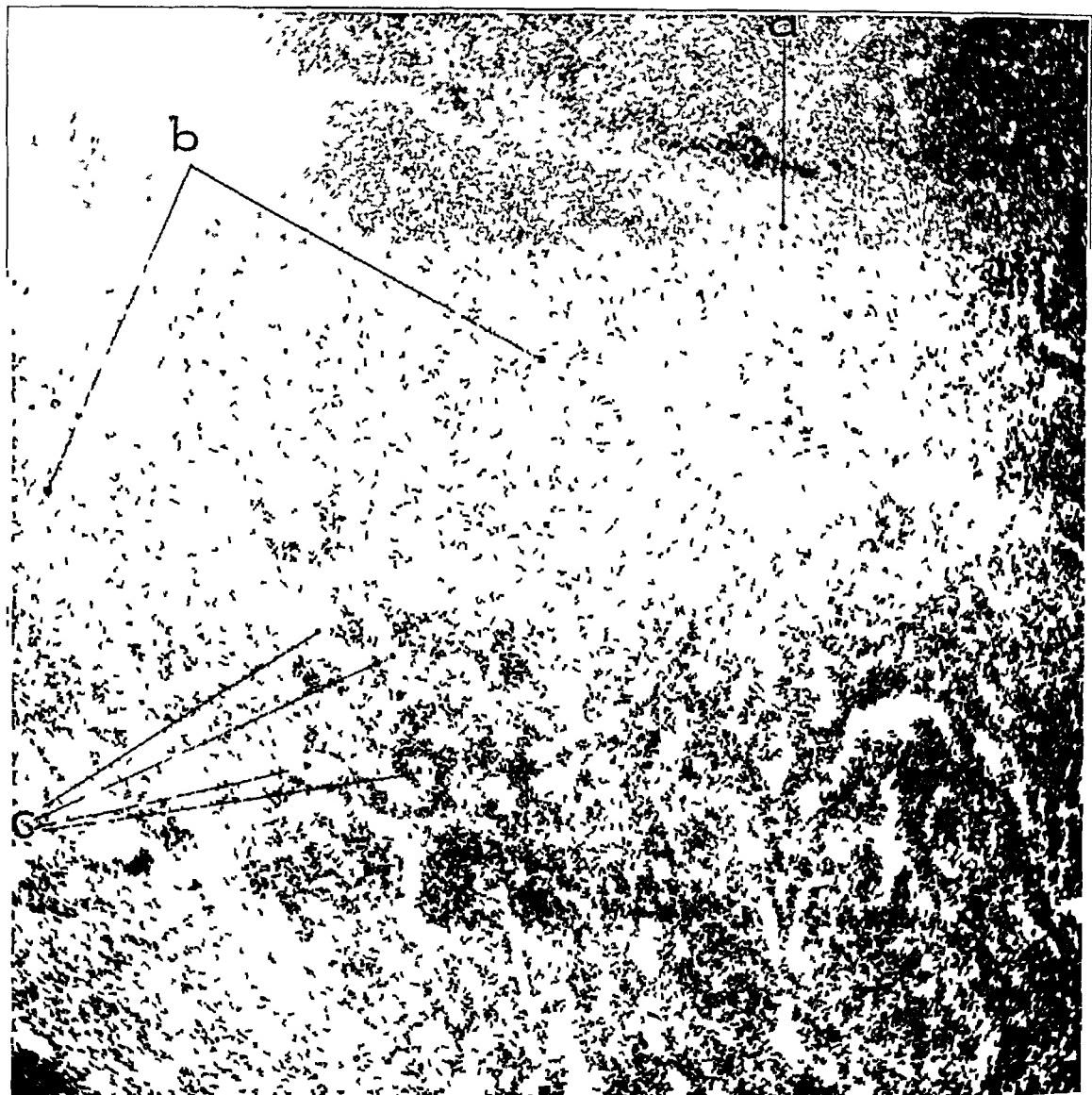


Fig 5.—The bottom of a crypt with a localized chronic ulceration. This tonsil was removed as a possible focus that was causing an infectious arthritis, with a clinical recovery. *a*, remains of epithelium lining the crypt, *b*, inflammatory cells in bed of an ulcer, *c*, rich network of capillary blood and lymph channels in bed of ulcer.

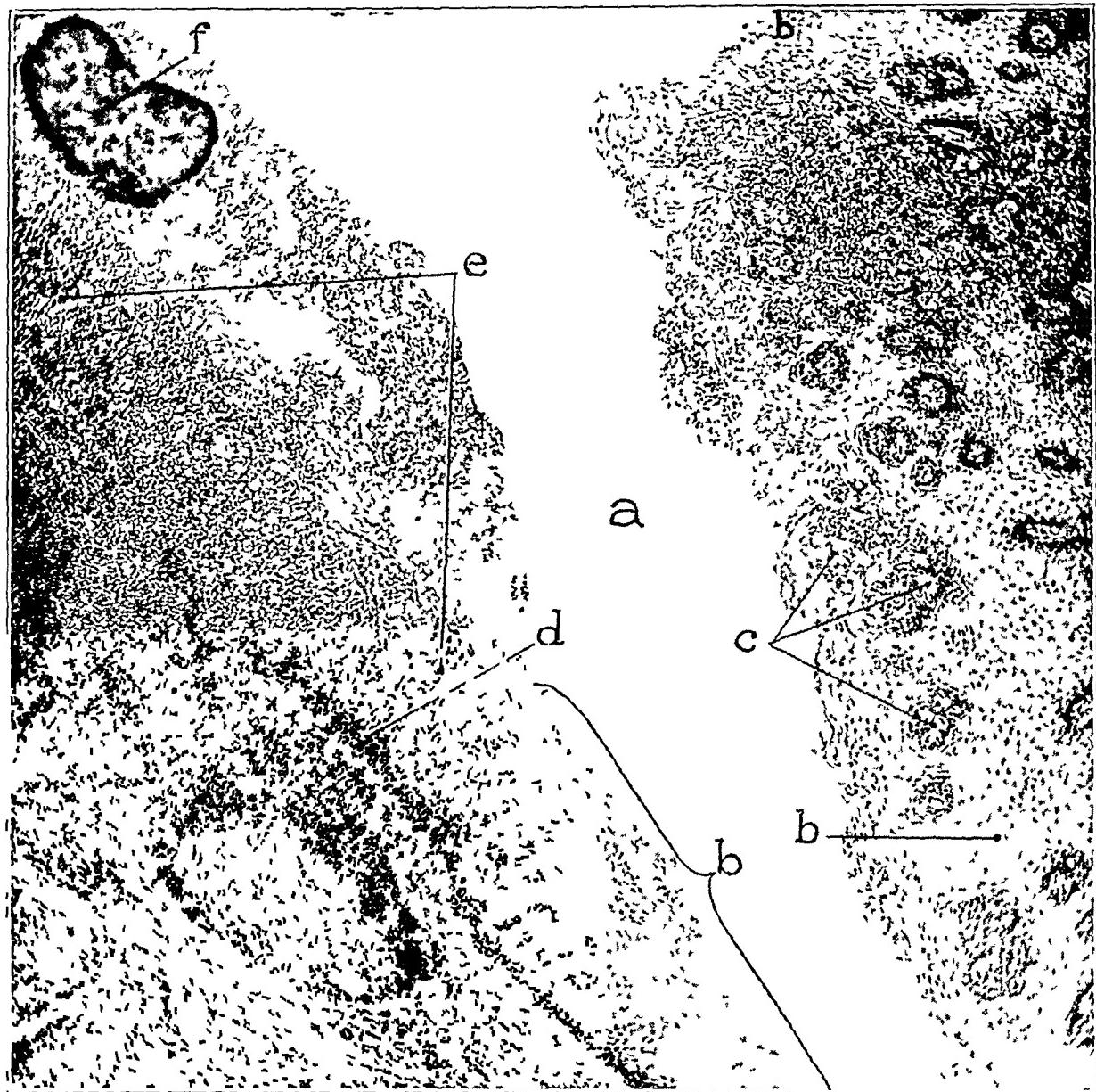


Fig 6.—Section of a tonsil removed for infectious arthritis, with a clinical recovery, *a*, lumen of crypt, *b* to *b*, normal epithelium lining crypt, *c*, capillaries containing red blood cells, *d*, inflammatory cells in the base of an ulceration, *e*, area of destruction of epithelium, *f*, a clump of bacteria and cellular debris in lumen of crypt

an exceptionally rich network of blood vessels in its base. It is easy to imagine, but difficult to prove, that from time to time emboli containing bacteria enter the blood stream direct, in addition to those that gain entrance through the large lymphatic channels in the tonsil.



Fig 7.—Localized ulceration in a crypt. Tonsil removed from a patient with infectious arthritis, with a clinical cure. *a*, lumen of crypt, *b*, area of ulceration, *c*, normal crypt epithelium.

It is well known that in many cases of infectious arthritis a hemolytic streptococcus may be cultivated from a gland removed from the groin, the popliteal space, the axilla or the neck. Blood removed from an arm vein in such cases rarely contains organisms, but it is possible that if blood were removed from the jugular vein a positive culture might

result in those cases in which the focus of infection is located in the upper respiratory passages

It also seems reasonable to suppose that a careful microscopic search might disclose ulcerations in the lymphatic tissue in the intestinal

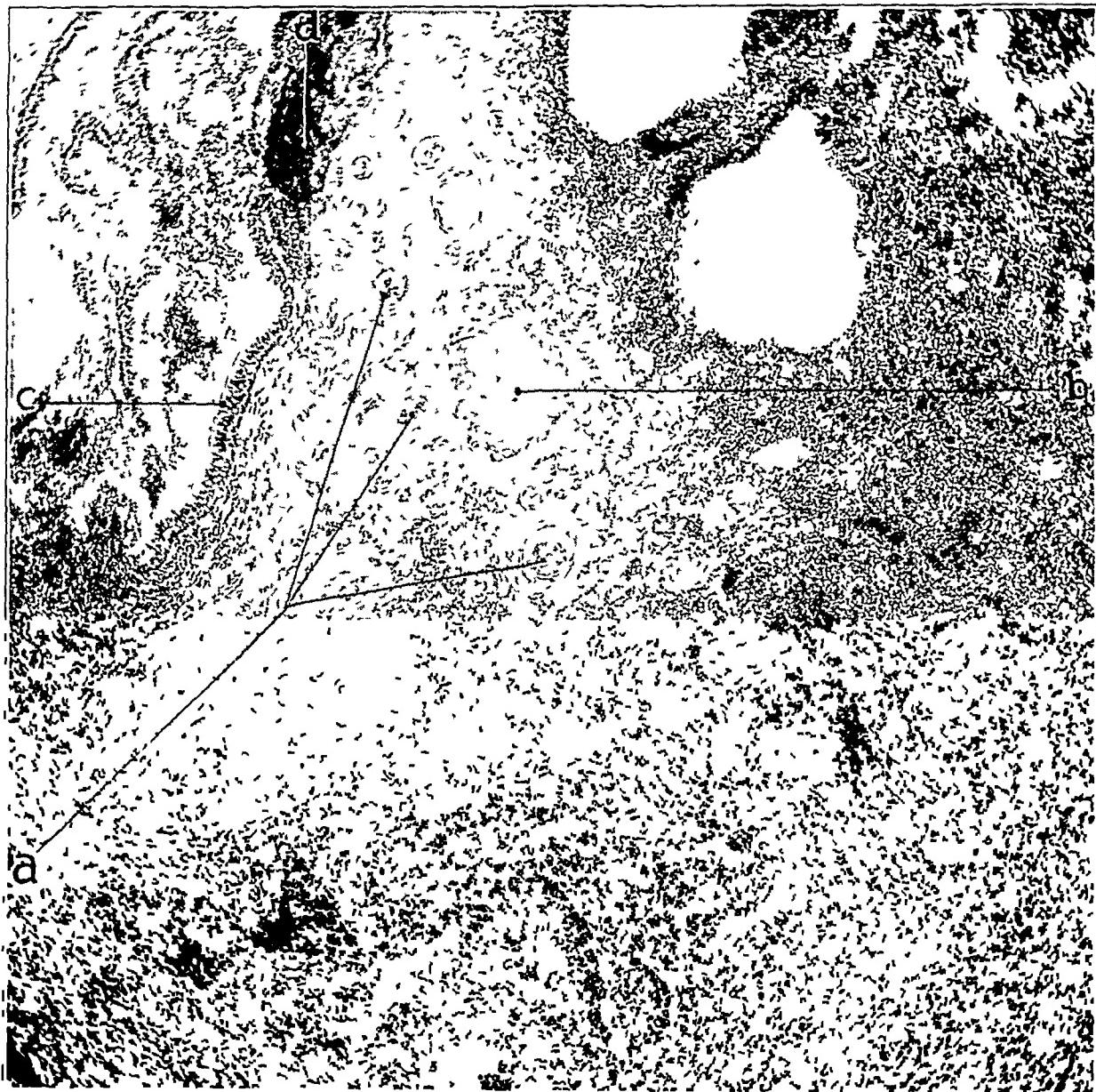


Fig 8.—Chronic infection of the lymph-adenoïd tissue in the nasopharynx. A chronically infected nasopharynx is of equal importance with the tonsil as a focus of infection. *a*, small arteries containing thrombi, *b*, a normal vein filled with blood, *c*, ciliated epithelium lining a crypt, *d*, accumulation of inflammatory cells.

wall similar to those that occur in the crypts of the tonsils. A digestive disturbance is usually associated with every acute infection and with many chronic infections of the tonsils, adenoids and accessory nasal

sinuses. It is possible that the lymphoid tissue of the intestinal tract is infected with the swallowed discharge. In children, particularly, a colon bacillus pyelitis frequently follows an acute upper respiratory infection. Whether this is due to an exacerbation of a low grade chronic infection in the urinary tract or to a hematogenous infection is not known.

SUMMARY

The epithelium lining the crypts of the tonsil differs from that covering the surface. The crypt epithelium has papillae and a rich network of capillaries, while the epithelium covering the surface of the tonsil has but few capillaries and no papillae. A destruction of the crypt epithelium, in whole or in part, is the most common pathologic finding in chronic tonsillitis. In the majority of the tonsils examined microscopically, the ulcerated areas in the crypts have healed, in others there are definite chronic ulcers.

These ulcerated areas are surrounded by an accumulation of plasma cells, lymphocytes and leukocytes. There is a rich network of thrombosed capillaries and lymph channels around the margins of the ulcers, and the conditions seem favorable for the passage of organisms into the lymphatic system and the liberation of infected emboli into the blood stream. We have found such ulcerated areas most frequently in the tonsils of individuals suffering from infectious arthritis, and least frequently in those in whom the tonsils were removed for acute rheumatic fever and chorea. A few of the arthritic patients whose tonsils show histologic ulcers in the crypts have no palpable enlargement of the cervical lymph glands, and the findings in these cases suggest a direct blood stream infection. This supposition is strengthened by the fact that this type of lesion in the crypt is found most commonly in patients with a variety of arthritic involvement (infectious arthritis) that responds most frequently to the removal of an infected focus and general hygienic measures.

HISTOLOGIC HYDROGEN-ION STUDIES OF THE KIDNEY

EDWARD J STIEGLITZ, M.D.

Fellow in Medicine, National Research Council

CHICAGO

Studies of nephritis and renal function have included much work on the blood and urine, especially that done in connection with hydrogen-ion concentrations. They have included little work on the secreting cells, however. The present studies were undertaken in an attempt to determine what parts of the uriniferous tubules are responsible for an acid or alkaline reaction of the urine. It was felt that the localization of such determining function would yield data of value concerning the normal and pathologic physiology of the kidney. The hydrogen-ion concentrations in the secreting cells and in the urine were determined simultaneously under varying conditions. The following phases of the problem have been considered: 1. Where is the reaction of the urine determined? 2. How is it determined? 3. What effect has altering the reaction of the urine on the normal findings? 4. What effect has nephritis on the normal findings? 5. What effect has alkali therapy on the findings in nephritic kidneys? These investigations were carried out by the use of vital indicator dyes introduced into the living animal.

In 1885, Dresser¹ used dyes *in vivo* for their indicator reaction, injecting acid fuchsin into frogs. In an acid solution the dye is red, in alkaline, yellow. He found that following an injection of acid fuchsin the urine became brilliantly red, but no red cells were demonstrable in the kidney. After repeated injections the cells of the convoluted tubules and the straight tubules became red. Fischer² explains this on the basis that repeated injections of acid fuchsin, which is a weak acid, injure the cells and thus cause an acid reaction. Dresser also found the cells stained red when the renal artery was tied, and the cells asphyxiated Nussbaum³ and Heidenhain,⁴ working with indigosulphonate, obtained essentially similar results. Grutzner⁵ found that the glomeruli could also be stained with indigosulphonate, showing an acid reaction, when sufficient asphyxia was produced in the kidney. These results and Fischer's conclusions are essentially in accord with those described below.

* From the Hull Laboratory of Anatomy and the Hull Laboratory of Physiology, University of Chicago.

1 Dresser Ztschr f Biol **21** 41, 1885 Ibid, **22** 56, 1886

2 Fischer Edema and Nephritis, New York, John Wiley & Sons, 1915

3 Nussbaum Pflüger's Arch **16** 141, 1878

4 Heidenhain Pflüger's Arch **9** 1, 1875

5 Grutzner Pflüger's Arch **24** 461, 1882

Harvey and Bensley,⁶ Edinger,⁷ Frankel⁸ and others have used similar indicator dye methods in connection with the secretion of hydrochloric acid or its precursor by the gastric mucosa. Harvey and Bensley used neutral red successfully, and Edinger sodium alizarinate Hoeber⁹ and Sorensen¹⁰ give excellent discussions on indicator dyes as applied to physiologic work. Marshall and Vickers,¹¹ in studying the renal secretion of phenolsulphonephthalein, observed the dye in the convoluted tubules of the kidney of the dog.

METHODS

The first problem which presents itself in undertaking to determine intracellular hydrogen-ion concentrations by means of vital indicators is the choice of the dyes. An indicator to be of use must fulfil all the following conditions. It must be nontoxic, it must be readily absorbed by living cells and therefore be soluble in tissue fluids, it must

Nature of Color Changes and Hydrogen-Ion Concentrations at Which These Occur

Dye	Acid			Alkaline		
	pH	Color	Relative to H ₂ O	pH	Color	Relative to H ₂ O
Neutral red	10 ⁻⁶ s	Red to blue	Neutral (pH 10 ⁻⁷)	10 ⁻⁸	Orange to yellow	Alkaline
Sodium alizarinate	10 ⁻⁶ 10 ⁻⁸ 10 ⁻¹⁰	Yellow Orange Magenta	Acid Alkaline Alkaline	10 ⁻¹² 10 ⁻¹⁴	Purple Blue	Alkaline Alkaline
Azolitmin	10 ⁻⁶	Pink	Slightly acid	10 ⁻⁷ 10 ⁻⁸	Violet Blue	Neutral Slightly alkaline

show a marked, readily detected color change, and last, the end-point must be at a hydrogen-ion concentration within the range of the changes in living cells. The last requirement is the most essential one.

Three dyes were found to be of great value and were used in this series of experiments. Several dyes were tried and discarded, especially because the end-point of color change was at too high a hydrogen-ion concentration. For example, Congo red, methyl red, and dimethylamidoazobenzol have end points between pH 10⁻³ and pH 10⁻⁶, so that they give an alkaline reaction in pure distilled water. Binschadler's green was useless because of its toxicity. The three dyes used successfully were neutral red, sodium alizarinate and azolitmin.

6 Harvey and Bensley Biol Bull 23 225, 1912

7 Edinger Arch mikro Anat 17, 1879

8 Frankel Arch f d ges Physiol 48 63, 1891

9 Hoeber Physikalische Chemie der Zelle u Gewebe, 1914, pp 170-173

10 Sorensen Biochem Ztschr 21 131 and 304, 1909

11 Marshall and Vickers Bull Johns Hopkins Hosp 34 1, 1923

Azolitmin has the same color changes as litmus, and can be obtained as a pure dye. It changes color at the same level as neutral red, about p_H 10⁻⁷, or at the true neutral point of pure distilled water. Sodium alizarinate is somewhat less satisfactory. It is difficult to obtain uniformly pure alizarin. Sodium alizarinate is soluble and purple in color, on the addition of acid, the more insoluble alizarin is precipitated as an orange dust. The sodium salt was prepared (KR 8,36) from alizarin by the addition of sodium hydroxid to an excess of the alizarin dye, and the filtrate used. These three dyes are nontoxic, are readily soluble in water, are absorbed by the cells and secreted into the urine. Throughout the recorded results the terms acid or alkaline are used relative to the p_H of pure distilled water at 10⁻⁷.

Intravenous injection of concentrated solutions of the dyes was found to be the most satisfactory method of administration. Perfusion with dilute solutions introduced several sources of error, by asphyxia of the kidney and altering the normal physiologic state. The animals used were rabbits, dogs and a few white mice. In the latter, subcutaneous injection of the dyes was resorted to. Rabbits were used, first, to determine the efficiency of the dyes and, secondly, because they have a normally alkaline urine in contradistinction to the acid urine of the omnivorous dog. It is essential that the kidneys be examined immediately after death, because about five minutes after death the reaction of the tissues begins to change as a result of autolysis.

RESULTS

The hydrogen-ion concentration in the kidney cells and urine were determined in thirteen normal rabbits by the use of the three dyes mentioned above. The results in all these experiments are essentially identical, and the protocol of one representative experiment will suffice.

EXPERIMENT KR 33.—Fifteen cubic centimeters of a saturated filtered solution of azolitmin in distilled water was injected into the marginal ear vein of a male rabbit, weighing 1,300 gm., without any apparent toxic effect. A few drops entered the subcutaneous tissue, where the purplish color became blue (alkaline). The animal was killed thirty minutes later by having its throat cut. Necropsy was performed at once, and the kidneys examined both with the naked eye and by means of sections of the fresh tissue (made with a double bladed Valentine knife) studied with a low power lens.

The findings were: 1. The bladder urine was blue (alkaline). 2. A blue color was present in the medulla throughout. This fluid was readily expressed by light pressure and was evidently alkaline urine in the collecting ducts. 3. The cortex was red (acid). The red dye was most concentrated in the cells of the convoluted tubules. 4. No dye reaction was demonstrable in the glomeruli. 5. The outer medullary zone was distinctly reddish (acid). 6. The medullary rays were grossly bluish (alkaline), but a few loops of Henle which could be fairly accurately identified in the fresh sections contained red (acid) cells.

As noted above, the findings in this whole series were uniformly the same in all the normal animals having an alkaline urine. It is to be noted that when the urine is alkaline (p_H less than 10⁻⁷) the cells of the convoluted tubules and the outer medullary zone show an acid reaction. The outer medullary zone differs anatomically from the rest of the medulla only by the additional presence of numerous loops of Henle. The medulla contains an alkaline urine, which is readily pressed out, leaving no dye in the cells of the collecting tubules, but the acid dye reaction in the outer medullary zone cannot be so altered. On study of the fresh sections the dye is seen to be intracellular there, but not so in the collecting tubules of the medulla proper. Therefore, it may be concluded that the acid reaction of the outer medullary zone in these animals with an alkaline urine is due to acid cells of the loops of Henle. The findings in the medullary rays confirm this.

The results of similar experiments with normal dogs show essentially a completely reversed picture. Five normal animals were successfully studied, with uniformly consistent results in all the experiments. Two typical protocols of this series follow —

Experiment KR 18 —A young male dog, weighing 10 kg., was fed entirely on meat, largely raw, for four days before the experiment. No water was given on the day before the experiment, but 300 cc of water were given one hour before starting the experimental procedure. This preliminary procedure was carried out to insure a rather concentrated and strongly acid urine during diuresis.

The animal was anesthetized with ether, and the left external jugular vein exposed. Into this 30 cc of 1 per cent neutral red in distilled water (0.3 gm of dye) were slowly injected. The abdomen was then opened and the right kidney exposed to the air. The kidneys were removed ten minutes after the end of the injection, after bleeding the animal to death.

The findings were 1. The bowels and kidneys showed considerable red color externally. 2. The bladder urine contained a little dye, purplish red (acid). The bladder was full. 3. The renal medulla, seen in surfaces made by cutting, contained purplish red (acid) urine in the tubules. This color was most intense at the lower border of the outer medullary zone. The cells of the collecting tubules were white after expressing the urine. 4. In the cortex the reaction was everywhere yellow (alkaline), both to the naked eye and microscopically in the fresh tissue sections. The convoluted tubules were yellow (alkaline) in reaction throughout. 5. The medullary rays contained some red (acid) urine, but not in all the tubules. This red color was confined to the lumina of the tubules there. 6. The outer medullary zone was not clearly demarcated.

Conclusion With an acid urine, the cortical reaction was everywhere alkaline.

Experiment KR 51 —A normal female dog, weighing 8 kg., was anesthetized with ether. The left external jugular vein was then exposed, and 40 cc of a saturated solution of azolitmin in distilled water was injected intravenously with no appreciable reaction. Ten minutes later the carotid artery was cut, and the dog bled to death. While bleeding the abdomen was opened and the kidneys removed immediately on the death of the dog.

The findings were 1. The bladder urine was reddish (acid). 2. The urine in the renal pelvis was red (acid). 3. The urine in the medullary collecting tubules was red (acid) on both sides. 4. The cortices of both kidneys were

bluish (alkaline), but in some places the intensity of the blue was greater than in others. 5 The outer medullary zone in both kidneys was decidedly bluish (alkaline). In sections made with a Valentine knife it was seen that this blue dye was present only in certain tubules, while others which were directly continuous with the purely collecting tubules of the lower medulla contained no dye in their cells. Therefore the tubules with the alkaline cells must be Henle's loops. 6 One lobe, or pyramid with the cortex above it, showed a reversed reaction bluish (alkaline) urine in the papilla, reddish (acid) cortex—convoluted tubules—and reddish (acid) outer medullary zone.

Conclusions 1 This experiment confirms the normal findings in the dog that with an acid urine the convoluted tubule and loops of Henle cells are alkaline, with azolitmin in place of neutral red. 2 One or more lobes of a kidney may be secreting an alkaline urine, while the rest is secreting an acid urine, with an excess of the acid form, making the mixed result (bladder or ureteral urine) acid.

The observation that one or more lobes of a kidney may be secreting a urine of the opposite reaction was also noted in two other experiments with dogs (KR 38 and KR 41), in both of which sodium alizarinate was used. This is of considerable interest, as heretofore it has been largely assumed that even if the whole kidney does not secrete uniformly in the quantitative sense, it at least does so qualitatively. These observations show that that is not the case. The absence of this phenomenon in the rabbit is undoubtedly due to the fact that this animal has a unilobar kidney.

Two other phenomena were studied in normal animals. One was the intensification of the normal alkaline reaction of the urine in the rabbit by the administration of sodium bicarbonate, and the other the alkalinization of the dog's urine by the same means. Protocols of two such experiments follow.

Experiment KR 20—Twenty cubic centimeters of 10 per cent sodium bicarbonate was put into the stomach of a young male rabbit, weighing 1,200 gm., by catheter. After fifteen minutes 10 cc of 1 per cent neutral red were injected into a marginal ear vein, with no apparent toxic effect. The animal was killed ten minutes later by having its throat cut, and necropsy was performed immediately.

The findings were 1 The bladder urine was yellow (strongly alkaline). 2 The medullae were also yellow (strongly alkaline), due to the urine in the collecting tubules, which was readily expressed. 3 The cortices contained much purplish red (acid) dye. With the microscope it was seen that this color was in the convoluted tubules, and that the bluish (strongly acid) tint was decided. 4 The medullary rays in the cortex were yellow (alkaline), in contrast to the bluish red (strongly acid) reaction in the convoluted tubules. This alkaline reaction was in the lumina of the collecting tubules. The acid reaction of the convoluted tubules was more marked in this experiment than in the normal animals who had not received alkali.

Experiment KR 60—A young male terrier, weighing 6.5 kg., was given 18 gm. of sodium bicarbonate in 350 cc of tap water by a stomach tube. The animal did not vomit. One hour later the dog was anesthetized with ether, the right femoral canal opened and the femoral vein exposed. This was cannulated, and 250 cc of 0.5 per cent neutral red in physiologic sodium chloride were introduced into the circulation, without an appreciable toxic effect. Ten minutes later the abdomen was opened, and the dog was killed by the cutting of the aorta. The kidneys were removed at once and examined.

The findings were 1 The bladder urine was cloudy and orange (alkaline) 2 Both kidneys were small, the capsules stripped readily, leaving smooth glistening surfaces Surfaces made by cutting showed no gross anatomic changes 3 In the medullae the tubules contained an orange red (alkaline) urine, which was easily squeezed out After pressing this out, the medullary tissue was white 4 The outer medullary zones were conspicuous, sharply demarcated and raised on cut surface They were purplish red (acid) 5 The cortices were also purplish red (acid), and most of this color was in the labyrinthian portion In sections made with a Valentine knife it was seen that the dye was in the cells of the convoluted tubules The intensity of the color was greatest in the cortex

Conclusions When the reaction of the urine in the dog is changed from the normal acid to an alkaline one, the reaction of the secreting cells is changed from alkaline to acid

Thus it is demonstrated that exaggeration of the intensity of the normal alkaline reaction of the rabbit's urine causes an increased intensity of the acid content of the secreting cells In the normal animal it was invariably found that the reaction of the urine was the opposite to that of the cells of the convoluted tubules and Henle's loops This relationship is retained even though the reaction of the urine is reversed by the administration of alkali It is of considerable clinical significance that the renal cells are acid when secreting an alkaline urine

After several unsuccessful attempts to obtain a normal animal secreting a neutral urine ($p_H 10^{-7}$), one was obtained The results of this experiment are recorded in Experiment KR 66

Experiment KR 66—A small male dog, weighing 8 kg, was given a meat free diet for two days and then very salty food containing also some sodium bicarbonate Just before the experiment the dog was allowed to drink a large amount of water One hour later the animal was anesthetized with ether, the left external jugular vein exposed and 50 c.c. of a saturated solution of azolitmin in distilled water injected intravenously Ten minutes later the animal was killed by cutting the abdominal aorta The kidneys were removed at once and examined

The findings were 1 The bladder urine was violet (neutral) 2 Both kidneys were grossly normal throughout 3 Both medullae contained purplish red or violet (neutral) urine, which could be readily expressed with light pressure 4 The outer medullary zones were sharply defined in both kidneys, and were dark, purplish red (neutral) This part of the kidney contained more dye than any other 5 The cortices were purplish red (neutral) throughout, and the dye was almost all, if not all, in the cells of the convoluted tubules

Conclusions With a neutral urine ($p_H 10^{-7}$) in the dog, the reaction of the kidney secreting cells is also neutral

The experiments reported above are typical examples of the results obtained with about twenty-five normal animals The findings were repeatedly confirmed by using all three of the indicator dyes In no instance were results obtained which deviated from the general picture It may be safely concluded that the secreting cells of the normal kidney have the opposite reaction to the urine, when the latter is acid, the cells of the convoluted tubules and Henle's loops are alkaline, and when the urine is alkaline the reversed reaction obtains in the cells Further-

more, exaggeration of the alkalinity of the urine leads to an increase in the intracellular acidity. The whole kidney does not function identically at a given time in the qualitative sense, but one part may be secreting an alkaline urine while the rest forms an acid one. Lastly, when the urine is just neutral, the cells are also neutral.

The hydrogen-ion concentrations of cells and urine were simultaneously studied in eighteen animals with experimentally induced nephritis. Seven rabbits were studied, in six of which an acute tubular toxic nephritis was produced by the subcutaneous injection of mercuric chloride or sodium potassium tartrate¹² twenty-four hours before the injection of the indicators (Experiments KR 40, 42, 45, 46, 48 and 49). In these experiments each of the three dyes was used, and further control was obtained by the use of the same dye for each of the two forms of toxic nephritis. The results were uniform in all of the experiments, and a protocol of one will suffice as an example.

Experiment KR 48—A large female albino rabbit, weighing 1,800 mg., on July 15, 1923, at 4 p.m., was given 2 gm of sodium potassium tartrate (Rochelle salts), injected subcutaneously into the back. The animal was returned to the cage. On July 16, at 4:30 p.m., the animal was lying quietly in the cage, apparently quite toxic. There was some diarrhea. Twelve cubic centimeters of 1 per cent neutral red in distilled water was injected into the marginal ear vein, with no reaction. The animal was killed twenty minutes later by decapitation.

The findings were: 1. The bladder urine was bluish red (acid). 2. The two kidneys were alike, swollen, pale and opaque, bulging when the capsule was stripped. 3. The medullary pyramids contained bluish red (acid) urine, which could be easily pressed out of the ducts. 4. The outer medullary zones were distinctly orange to yellow (alkaline). With the microscope the dye was here seen in the cells of Henle's loops. 5. The cortices were deep purplish red throughout (acid). Fresh sections localized the reaction here as being in the cells of the convoluted tubules. 6. Formaldehyde fixed frozen sections stained with hematoxylin and eosin showed an acute degenerative process in the convoluted tubules, with no apparent change in the glomeruli or loops of Henle.

The fact that the loops of Henle retained their normal relationship of the opposite reaction to that of the urine is of interest. The histologic study and previous observations support the impression that these cells are not severely damaged by the intoxication. It has long been known that the tartrates injure primarily the convoluted tubules.¹³ One rabbit with spontaneous nephritis was encountered (KR 14) in which the entire kidneys, urine and cells alike, were acid in reaction. This animal had distemper, some ascites and diarrhea. Paraffin sections of the kidney revealed a thinned cortex, with distended tubules lined with flattened cells and some acute increase in the connective tissue and round cells. One large area in the cortex, extending from the renal

12 Underhill, Wells and Goldschmidt J Exper Med 18 317, 1923 Stieglitz Am J Anat 29 33, 1921

13 Stieglitz Am J Anat 29 33, 1921

capsule to the arcuate arteries was almost entirely replaced by round cells. In dogs similar studies were undertaken, and in five animals (KR 54, 62, 63, 64, and 65) an acute toxic tubular nephritis was induced. The results of these experiments are essentially similar to those observed in the rabbits. A single typical protocol will suffice.

Experiment KR 63—A male dog, weighing 9 kg., on Aug 21, 1923, was placed in a metabolism cage with plenty of water. On August 22, the urine was acid. No albumin, no casts or sugar were present. The specific gravity was 1.034. The animal was given a subcutaneous injection of 0.1 gm. of mercuric chloride.

On August 23, the dog was very quiet and listless. Urinalysis revealed albumin, a few casts, acid, no sugar. The animal was anesthetized with ether, and 150 c.c. of 1 per cent neutral red in distilled water were given into the right femoral vein by gravity through the cannula. Five minutes after the end of the injection the abdomen was opened, and the animal was killed by bleeding from the aorta. The kidneys were removed at once and examined.

The findings were: 1. The bladder was distended with acid urine, containing considerable albumin. 2. The two kidneys were alike—very soft, moist and opaque. 3. The medullae contained purplish red (acid) urine which was easily expressed from the ducts by light pressure. 4. The outer medullary zones were clearly demarcated and distinctly bluish red (acid). This color could not be pressed out. 5. The cortices were purplish red (acid) throughout, the color being most concentrated in the labyrinthian portion. 6. The medullary rays contained little dye. 7. Frozen sections stained with hematoxylin and eosin showed an acute tubular degeneration involving chiefly the convoluted tubules. The glomeruli appeared to be unaltered.

Conclusions In acute toxic (mercuric chloride) nephritis in the dog, as in the rabbit, the urine, loops of Henle and convoluted tubules are all acid.

These results confirmed the findings in nephritic rabbits. Two dogs (KR 43 and KR 50) with a long standing chronic unilateral nephritis were similarly studied, the unaltered kidney acting as the normal control. The findings in these experiments are essentially similar to those in the acute nephritis.

Experiment KR 45—A male dog, weighing 10 kg., on May 26, 1923, was anesthetized with ether, and under careful aseptic conditions the right kidney was exposed through a posterior nephrotomy incision, a "bull dog" clamp was placed on the right renal artery and left on for fifteen minutes. After its removal the kidney was slipped back into place and the wound closed in layers. The anesthesia was carried throughout without difficulty, and the dog recovered rapidly. On May 27, the dog was recovering well. Urinalysis showed blood + + +, albumin + +. From May 29 to June 19, the dog continued in excellent condition, the wound closing completely. The urine continued to show albumin and casts. Hematuria disappeared about June 1. On July 6, the weight was 8 kg. There have been no manifestations of intoxication or edema. On July 8, urinalysis revealed albumin +, one or two casts, acid, specific gravity, 1.023. On July 9, the dog was anesthetized with ether, and 50 c.c. of a saturated solution of sodium alizarinate were injected intravenously. After ten minutes the abdomen was opened and the aorta cut. The kidneys were promptly removed and examined.

The findings were: 1. The right (injured or nephritic) kidney was firmly bound down by fibrous adhesions, which were especially marked on the posterior surface, at the pedicle and upper pole, the latter being firmly adherent to the hepatic capsule. The renal capsule was stripped with difficulty, leaving a rough,

granular, rather dry yellow surface. The cortex was moderately narrowed and quite firm. The dye reaction was the same throughout all parts of the kidney, yellow or acid. The urine in the collecting tubules of the medulla and in the renal pelvis was bright orange yellow (acid). The cortex was also yellow (acid), and in sections made with a Valentine knife, examination with a low power lens revealed that the dye here was chiefly in the cells of the convoluted tubules. The outer medullary zone was also yellow (acid) in reaction. Blocks of tissue were fixed in 10 per cent formaldehyd solution.

2 The left (uninjured or control) kidney was readily removed from the surrounding fat. The renal capsule stripped easily, leaving a smooth glistening surface. The kidney was cut through in many places and showed yellow to orange (acid) urine in the pelvis and collecting ducts of the medulla. The outer medullary zone contained many vertical purple (alkaline) markings, between which were whitish yellow tissue. With the microscope the purplish (alkaline) tubules appear to be loops of Henle. In the cortex the dye was most concentrated in the outer zone, where it was purple (alkaline), and in the cells of the convoluted tubules (microscopic examination of fresh sections). No gross pathologic condition was seen. Pieces of this kidney also were fixed in 10 per cent formaldehyd solution.

3 The bladder urine was acid, and contained albumin and casts. 4 No other gross pathologic findings were detected by a complete necropsy. 5 Histologic findings of the fixed tissue, stained with hematoxylin and eosin showed Right or damaged kidney. The cortex was very thin, many tubules were dilated, there were some connective tissue scars, but no necrotic tissue was seen. The cells appeared to be edematous, staining poorly with eosin. Many of the tubule cells were desquamated. The left or control kidney was normal.

Conclusions. In a kidney damaged forty-four days before by a transient asphyxia, the hydrogen-ion concentration of the cells and urine are similar to those found in an acute nephritis, the damaged cells and urine both being acid, while in the opposite control kidney of the same animal the reaction of the cells was alkaline in the normal relationship to the acid urine.

The findings in Experiment KR 50, in which the same procedures were carried out, were identical. Several experiments dealing with acute asphyxia of one kidney were carried out (KR 52, 53, 58, 59). The fact that asphyxiated cells become temporarily acid in reaction has long been known, and this was again demonstrated in these experiments. The dogs were anesthetized with ether, the indicator injected intravenously, a renal pedicle exposed and the renal artery clamped for fifteen minutes. After the removal of the clamp the dogs were bled to death and the kidneys examined at once. In all instances the asphyxiated kidney was acid in reaction through the whole of its substance, urine and cells alike, whereas in the opposite normal control kidney the normal reaction pertained, acid urine and alkaline secreting cells. The appearance of both physiologic and anatomic evidence of nephritis as long as forty-four days after a transient fifteen minute asphyxia is of great importance. A rather careful search of the literature revealed no previous mention of such persistent damage. Asphyxia, even though transient, apparently results in serious injury which lasts for a considerable time.

An investigation of the effects of alkaline therapy on nephritic dogs was also undertaken. Three experiments (KR 62, 64 and 65) were performed. In one of these (KR 64), not enough alkali (sodium

citrate) was given to alkalinize the urine, and the findings were the same as those for the untreated nephritic animals. In Experiment KR 62, the animal was rendered nephritic with mercuric chlorid and given sodium bicarbonate by stomach tube to alkalinize the urine. Here it was found that the urine was alkaline, the outer medullary zone or loops of Henle acid, and that there was an almost complete absence of dye in the convoluted tubules. The absence of the dye there was probably due to the fact that the severely damaged convoluted tubules were not secreting the dye, throwing the burden on the loops of Henle. Alkalization of the urine in the normal animal causes the cells to become acid, and, as would be expected, it does not bring the reaction of the damaged cells to the alkaline side.

In Experiment KR 65 we were fortunate enough to just neutralize the urine of a nephritic dog. The protocol of this is reported below:

Experiment KR 65—A male dog, weighing 8 kg., on Aug 23, 1923, was thin and poorly nourished, otherwise he was apparently healthy. Urinalysis revealed no albumin, no casts, acid, specific gravity, 1.032. An injection of 0.08 gm of mercuric chlorid in 4 cc of distilled water was given subcutaneously. The animal was then returned to the metabolism cage. On August 24, the animal was very listless and quiet, and had a mushy diarrhea. Urinalysis revealed albumin ++, casts, acid, specific gravity, 1.038. At 1.30 p.m., the dog was given 15 gm of sodium bicarbonate by stomach tube in 300 cc of tap water. Ten or fifteen minutes later some of this was vomited. At 2 p.m., the animal was anesthetized with ether and 200 cc of 1 per cent neutral red in physiologic sodium chlorid introduced through a cannula into the right femoral vein. Five minutes later the animal was killed by cutting the aorta. The kidneys were examined at once.

The findings were: 1. The bladder was almost empty. The urine present was neutral (tested with both neutral red and azolitmin), p_H 10⁻⁷. Albumin was present. 2. Both kidneys were very soft and swollen. The cortical markings were not clear. 3. The medullary urine was red, neither orange nor purplish (neutral). 4. The outer medullary zone was clearly demarcated and contained much red (neutral) dye. 5. The cortices contained less dye, this was distinctly purple (acid) and was found in the degenerated convoluted tubules (fresh sections).

Conclusions By chance a nephritic kidney was studied which was secreting an exactly neutral urine. The urine and loops of Henle were both neutral as in a normal kidney under similar physiologic conditions, but the more severely damaged convoluted tubules remained acid. The great concentration of the dye in the cells of Henle's loops may be due to an excessively active secretion there, as the convoluted tubules were almost completely destroyed.

CONCLUSIONS

If we sum up the results obtained, and described above by some typical examples, it may be concluded that the following facts are established. When the kidney is secreting an acid urine, the cells of the parenchymatous tubules, both the convoluted tubules, proximal and distal, and the loops of Henle (thick limb) are alkaline in reaction. When the urine is alkaline these same cells are acid. When the alkalinity of the urine is exaggerated, the acid reaction of the cells is

increased, but it is impossible to say from the present studies to what degree. In all the nephritic kidneys studied the damaged cells presented an acid reaction, irrespective of the reaction of the urine.

DISCUSSION

The results recorded above indicate that the cells of the convoluted tubules and loops of Henle are essentially involved in the determination of the hydrogen-ion concentration of the urine. The reaction of the cells of these tubules bears a constant relationship to the reaction of the urine. They are the only renal cells in which the indicator dyes appear, and, as the dyes are secreted into the urine, they probably are passing through the cells. The fact that these cells invariably have the opposite reaction to that of the urine in the normal kidney is of considerable physiologic significance. It indicates that cells secreting an acid product retain temporarily the complementary basic components, making the cell content alkaline in reaction, and vice versa, when the cells eliminate an excess of basic products, they retain complementary acid components. We may imagine, for instance, this separation of base and acid to occur with the aid of the amphoteric proteins (amino-acids) of the cells which may combine with either the acid or the basic component of a hydrolyzed salt, in the form of protein salts. As these salts in turn are hydrolyzable in the way that all salts of weak bases or weak acids are, the reaction of the cell contents would be basic if the retained component is the base in combination with an acid radical of a protein, and the reverse would be true if the retained component is the acid combined with a basic radical of a protein. This conception is in line with the work of Nash and Benedict,¹⁴ who showed that the ammonia of the urine is formed in the kidney.

However, the question whether the convoluted tubules are elements of secretion has not been universally conceded. On the whole, there are two chief schools of thought concerning the mechanism of renal secretion. The one, first presented by Bowman,¹⁵ teaches that the glomeruli secrete water and some salts, and that the convoluted tubules concentrate the urine by the additional *secretion* of salts and nitrogenous products. The other school, founded on the theories of Ludwig¹⁶ and now largely supported by Cushny,¹⁷ maintains that the concentration of the urine is accomplished by the *reabsorption* of water and certain "threshold" bodies by the convoluted tubules. The gist of the situation therefore is Do the convoluted tubules *secrete* or *reabsorb*.

¹⁴ Nash and Benedict J Biol Chem **48** 463, 1921, ibid **51** 183, 1922

¹⁵ Bowman Philos Trans **57** 1842

¹⁶ Ludwig Mechanismus der Harnsecretion, Marburg, 1843

¹⁷ Cushny The Secretion of Urine, Monographs of Physiology, London, Longmans, Green and Co., 1917

so^b substances to or from the urine, or do they do both? That secretion does take place by these cells has been proven to be the case for several substances, such as urea¹⁸ and iron¹⁹. Cushny¹⁷ postulates that the chief source of the sodium hydroxid reabsorbed is from the phosphates,¹⁹ by hydrolysis of sodium phosphate. Richards²⁰ has recently added supporting data to the theory of reabsorption.

As regards the observations on hydrogen-ion concentrations in the cells and urine, the fact that the cells are of the opposite reaction to that of the urine may be interpreted by either theory. The cells may be alkaline because of a secretion of acid into the urine, or because of the reabsorption of bases, leaving the urine acid. But in the experiments on the rabbit in which the alkalinity of the urine was increased by the administration of sodium bicarbonate (KR 20), the acid reaction of the cells was also exaggerated. In view of the fact that greater alkalination of the urine by the addition of alkali leaves less acid to be absorbed from the urine by the cells, we are forced to the conclusion that the increased acidity of the cells is not due to reabsorption of acid from the urine. If, on the other hand, the cells are secreting a preponderance of bases from the neutral blood, a greater accumulation of intracellular acid might well occur. Therefore the observations recorded above serve to support the theory that the concentration of the urine and determination of the acid or alkaline reaction thereof is accomplished by secretion by the tubule cells.

In several instances in the nephritic animals studied it was noted that when the convoluted tubules were severely damaged and contained little dye, the loops of Henle were abnormally heavily laden therewith. It may be suggested that the loops of Henle take over the function of secretion when the convoluted tubules are so severely damaged. That this is so is by no means firmly established by these findings, but they strongly suggest such function on the part of Henle's loops.

In the nephritic kidneys it was invariably found that the injured cells were acid in reaction. Fischer² discusses the increased hydrogen-ion concentration of injured or asphyxiated tissue at length. He declares that the greatest hydrogen-ion concentration in the urine occurs in acute nephritis, and claims that the p_H of the urine is a valuable aid in making the prognosis of nephritic cases and in determining the condition of the kidneys. He has also shown that in nephritis the acid combining power of the blood is decreased. Araki²¹ and Zillessen²² showed that in asphyxiated tissue there is an accumulation of acid. These observations are entirely in accord with those recorded above.

¹⁸ Oliver Jour Exper Med **23** 301, 1916

¹⁹ Cushny Jour Physiol **31** 188, 1904

²⁰ Richards Am J Med Sc **163** 1, 1922, Am J Physiol **59** 184, 1922

²¹ Araki Ztschr f physiol Chem **15** 335 and 546, 1891, ibid **19** 473, 1894

²² Zillessen Ztschr f physiol Chem **15** 387, 1891

Fischer²³ maintains that edema and albuminuria are both the result of increased intracellular hydrogen-ion concentration, and that inhibition of secretion is a result of altered hydration capacity of the tissue colloids similarly induced. In this connection it is important to study the effects of alkali therapy. A normal kidney secreting an alkaline urine has acid cells therefore alkalinization of a nephritic person's urine should certainly not alkalinize the cells. In fact, the more alkaline the urine becomes the more acid are the cells and this might well increase the damage especially as the injured cells are already acid. Therefore it may be concluded that excessive alkaline therapy in nephritis is to be avoided and that the optimum condition to be obtained is *neutral zone* of the urine. If the urine is neutral, normal secreting cells will also be neutral, thus maintaining a reaction best suited for the repair and recovery of the injured cells. Clinical observations confirm these conclusions: over alkalinization not infrequently leads to an acute exacerbation of symptoms. Recently Brown and his co-workers²⁴ reported evidences of toxic nephritis associated with the alkalosis of duodenal obstruction.²⁴

SUMMARY AND CONCLUSIONS

1. When acid urine is being secreted the cells of the convoluted tubules and loops of Henle are alkaline in reaction (using $p_H 10^{-7}$ as the neutral point).
2. When alkaline urine is being secreted, these cells are acid.
3. When neutral ($p_H 10^{-7}$) urine is secreted, the cells are neutral also.
4. Increase in the alkalinity of the urine leads to increased acidity of the cells.
5. In the dog one or more lobes of a kidney may be secreting an alkaline the rest an acid urine simultaneously.
6. Alteration of the reaction of the urine causes a similar but opposite change in the reaction of the cells.
7. The reaction of the urine is controlled by the convoluted tubules and loops of Henle.
8. The reaction of the urine is determined by *secretion* of either an excess of acid or alkali by these cells.

²³ Brown, G. E., Eusterman, G. B.: Hartman, H. R., and Rountree, L. G.: Toxic Nephritis in Pyrictic and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tetany. Arch. Int. Med. 32:425 (Sept.) 1923.

²⁴ Since the paper was sent to the publishers H. F. Stratton, E. L. Rordenburg and Le'a E. Bonner have reported similar observations (J. A. M. A. 82:200 [Jan. 1924] 1924).

9 In nephritic kidneys the injured cells are acid in reaction, as is the urine, the normal relationship thus being destroyed

10 Alkalization of the urine in nephritic animals does not reverse the acid reaction of the cells

11 Alkali therapy in nephritis must not be carried to a point of alkalinization of the urine, as that tends to increase the intracellular acidity Neutralization of the urine, however, is desirable

AN IMPROVED AIR VALVE FOR APPARATUS USED IN BASAL METABOLIC WORK*

W. B. FULTON

WASHINGTON, D. C.

A special series of experiments¹ to determine the metabolic rate (this is done by the collection and analysis of expired air) of subjects exposed to varying temperatures and humidities was conducted under the supervision of Dr. R. R. Sayers and Dr. W. J. McConnell as part of a cooperative study of the physiologic effects of atmospheric conditions being made by the Bureau of Mines and the American Society of Heating and Ventilating Engineers. In this work a number of different types of valves were experimented with in order to select the one best suited. The deciding factor in selecting a valve for use in basal metabolic work rests with its ability to prevent any small amount of air from escaping around the edges of the valve when closed, which may be designated as "slip leakage".

Several types of valves are available which though satisfactory for use in certain breathing apparatus, could not be used in these experiments. The so-called 'mica-disk' valves must be kept in a horizontal position in order to function properly and it is impractical to do this with the subject lying down. There is a small amount of slip leakage with such a valve even when held in the horizontal position especially in slow and shallow breathing. This leakage has been eliminated by a few manufacturers who have inserted a small spring behind each disk, thus causing it to close more quickly and seat more firmly. Sometimes these disks have small ridges that permit leakage. Also the clicking sound in closing annoys some people. Other types of valves are those used with the mask type of oxygen apparatus and those with the mouthpiece type. In the mask type there is always the possibility of a leak around the mask and the increased dead air space gives rise to erroneous results while in the mouthpiece type it is impossible to have leakage and the dead air space is decreased to a minimum.

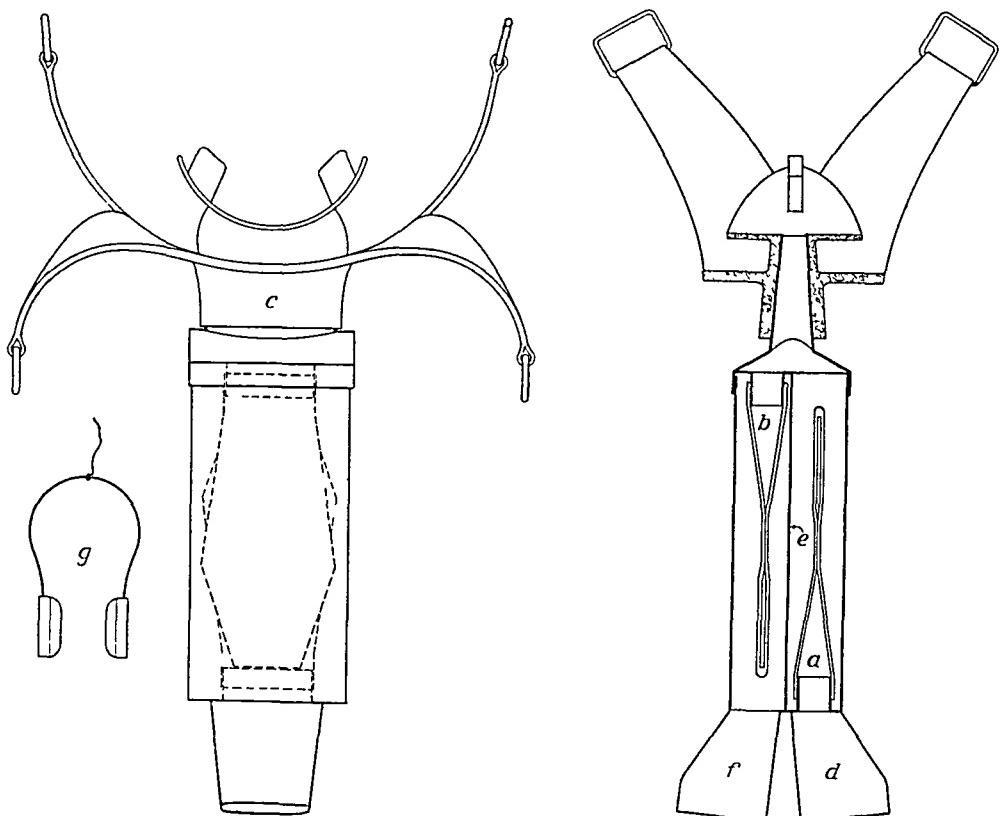
The use of the water valve is impracticable in basal metabolic work, because the difference in pressure causes a resistance to breathing which is objectionable.

I have developed an improved type of valve and used it successfully in the collection of samples for basal metabolic work at the Pittsburgh

* Published by permission of the Director Bureau of Mines, Department of the Interior.

1 Results of these investigations are shortly to be published.

Experiment Station This improved valve, worked out by the Bureau, is a modification of the Douglas² valve, which, with other valves similarly constructed, has been used in apparatus for basal metabolic work. Figure 1 shows the details of the valve used by the Bureau. *a* is the inhalation valve, and *b* is the exhalation valve, *c* is the rubber mouth piece, *d*, a pipe for rubber tube connection on the inhalation side, *e*, a tin partition between the two valves, *f*, a pipe for the rubber tube connection to the spirometer, and *g*, the nose-clip.



Double action rubber butterfly valve

The two butterfly valves (the rubber valves used for exhalation in the army type of gas mask) are placed parallel to each other but in opposite directions in a tin air-tight container $3\frac{3}{4}$ by $1\frac{3}{4}$ by $1\frac{1}{4}$ inches, and are separated by the tin partition. The valves are held at the base ends in such a manner that when not in use they are closed. The rubber mouth piece is coated with shellac, and is fastened securely to the container. Two pipes $\frac{7}{8}$ inch in diameter connect the container with the apparatus. These, because of their size, eliminate most of the resistance in the rubber tube connections.

² Douglas, C. G. A Method for Determining the Total Exchange in Man, *J. Physiol.*, March 18, 1911, p. 17

The valve described herein is simple in construction and inexpensive, yet it can be operated in any position without incurring the objectionable features of other types. It has been successfully used by the Bureau of Mines, and should be particularly well adapted to collecting samples of air for basal metabolic or allied work.

AURICULAR FIBRILLATION IN GOITER

E A BAUMGARTNER, M D , C W WEBB, M D
AND
HUBERT SCHOONMAKER, M D
CLIFTON SPRINGS, N Y

Recently Schoonmaker and Webb¹ reported a case of auricular fibrillation in a toxic adenoma of the thyroid. Because of the great improvement noted in all symptoms in this case and the rarity of this condition among our patients with goiter we thought it worth while to investigate the literature on this subject.

In looking through the literature we find that as yet not many cases have been reported in detail, and that as a rule there are only incidental references to cases of goiter in descriptions of various cardiac conditions. However, that auricular fibrillation is not rare in goiter is shown by Willius² who stated that at the Mayo clinic 7 per cent of patients with exophthalmic goiter and 9 per cent with hyperactive adenoma have auricular fibrillation on admission, and that these figures were doubled while the patients were under observation. Willius and Boothby³ in a more recent paper, gave figures of 22 per cent in exophthalmic goiter and 24 per cent in adenoma with hyperthyroidism. On the other hand, in their book on the thyroid gland, Crile and his associates⁴ described one case in some detail. Apparently, at the Cleveland clinic this condition was not found so frequently. Hamilton,⁵ in a series of 200 cases of goiter at a Boston clinic found eighteen cases of fibrillation among hyperthyroid cases, while Hamilton and Lahey⁶ stated that 10 per cent of patients with goiter have an absolutely irregular heart either as an established or recurrent condition.

1 Schoonmaker, H., and Webb, C W Report of a Case of Goitre (Adenomatous Type) Complicated by Auricular Fibrillation, Clifton M Bull 8 2, 1922

2 Willius, F A The Heart in Thyroid Disease, Ann Clin Med 1 269, 1923

3 Willius, F A , and Boothby, W M The Heart in Exophthalmic Goitre and Adenoma with Hyperthyroidism, Med Clin N Am 7 189, 1923, Heart in Exophthalmic Goitre and in Adenomatous Goitre with Hyperthyroidism, J A M A 80 1725 (June 9) 1923

4 Crile and Associates The Thyroid Gland, Philadelphia, W B Saunders Company, 1922

5 Hamilton, B E Clinical Notes on Hearts in Hyperthyroidism, Bost M & S J 86 216, 1922

6 Hamilton, B E, and Lahey, F H Differentiation of Hyperthyroidism and of Heart Disease from Neurasthenic State, J A M A 78 1793 (June 10) 1922

REPORT OF CASES

CASE 1—*History*.—A woman, aged 46, was admitted to the hospital on Jan 30 1922, complaining of rapid and irregular heart, nervousness, insomnia, loss of weight small physical endurance and recurrent attacks of abdominal cramp, nausea and vomiting. Her father had diabetes at the age of 76, and her mother died of pulmonary tuberculosis at the age of 33, otherwise the family history was negative. She had had some childhood diseases, typhoid fever, tonsillitis at the age of 40 and once previously. She had two normal healthy children.

Her present illness began ten years before (1912). In 1913, she had had an Alexander operation followed by cessation of the abdominal attacks, which however, began again in 1916, and necessitated two months' rest in bed. Six months later she had a recurrence of the attack followed by three months' rest in bed and dietary treatment. She had had many similar attacks, although they had been less severe since that time. A goiter was first observed in 1913. Toxic symptoms were clearly evident in 1916. It is not clear when auricular fibrillation developed but probably as long as six months before admission to the hospital.

Eamination.—On admission the patient could exercise only about 60 per cent of her normal capacity, and her heart was rapid and irregular. It never was definitely incompetent. Her weight was 115 pounds (52.2 kg.), about 10 pounds (4.5 kg.) below her normal weight. Her expression was anxious and she had large infected tonsils. Both lobes of the thyroid were enlarged and irregular the left more than the right. There was a soft systolic murmur at the apex of the heart which was somewhat enlarged and absolutely arrhythmic. The heart rate was 120 with a pulse deficit of 40. There were tremor of the fingers and rigidity of the abdomen. The laboratory findings were negative urine and Wassermann tests slight secondary anemia and a basal metabolism of 119 per cent.

Fluoroscopy of the chest revealed trachea slightly displaced toward the right and somewhat compressed above the level of the manubrium. The upper mediastinum showed a shadow suggesting an enlarged thyroid projecting down a very short distance in the upper mediastinum. The aorta was normal. The heart was moderately enlarged both to the right and left, with marked prominence of the auricular curve suggesting mitral disease. The action was rapid, tumultuous and decidedly irregular. The lungs showed increased fibrosis extending outward from both hilums with increase in the hilum shadows. The left apex had a suspicious appearance, but this appearance may have been caused by the substernal thyroid. The diaphragm was negative.

Several cardiograms were made. Before operation several were alike in showing no "P" deflection and the absence of ventricular rhythm as is characteristic of auricular fibrillation.

Treatment and Course.—The first thing attempted was to regulate the heart by rest in bed, the placing of an ice bag on the precordium, and the administration of tincture of digitalis, 15 minims (0.92 cc.) every four hours. The gastric symptoms were believed to be a part of the symptoms of toxic goiter. After four days the heart rate was quite constant and varied from 90 to 100 with no pulse deficit. It was then decided that no essential heart lesion existed and that the arrhythmia was toxic in origin. On February 17, thyroidectomy was performed. The left lobe was larger than the right, but both lobes were considerably enlarged, with several adenomas in each lobe. Practically all of the left and all but a small portion of the right lobe were removed. Convalescence occurred without complications. Three days after operation the heart became regular and has remained so. The maximum rate after cessation of fibrillation was 80, and the rhythm was normal.

A cardiogram was made five weeks after operation (March 23) which was normal, except for a flat or negative "P" deflection. This was thought to be

evidence of remaining thyroid toxicosis An electrocardiogram two months later (June 20) was normal

The patient left the hospital on April 7, much improved in weight and strength There were no murmurs in the heart, rhythm was normal, and the sounds were of good quality Six weeks later the patient appeared normal, she had gained 25 pounds (11.3 kg) and had no heart nor abdominal symptoms

Microscopic Examination—The microscopic sections showed some increase of connective tissue with hyalin changes and calcium deposits Some of these areas showed rather large vascular spaces The follicles were lined with low columnar cells A few were dilated, some with colloid, others were empty The section looked somewhat like a fetal adenoma with some angiomatous areas

Diagnosis adenoma, microscopically only slightly active

CASE 2—*History*—A man, aged 49, entered the hospital on June 13, 1922, complaining of a rapid heart and loss of weight He had had some of the childhood diseases, and influenza in 1920, there had been some flatulence, especially since 1917 after extraction of several teeth His present illness began a year before with attacks of palpitation He had had several attacks since then, the last one about two weeks before He had lost about 30 pounds (13.6 kg) in weight in the past six months

Examination—Physical examination revealed small tonsils and a small nodular mass in the region of the left lobe of the thyroid The heart was enlarged, rapid and absolutely arrhythmic, the apex rate 120, the pulse rate 90 The patient had a slight fine tremor of the hands

Fluoroscopic examination showed the trachea displaced to the left with a shadow extending into the left upper mediastinum The heart was slightly enlarged and rapid, with diminished force Laboratory tests revealed a negative blood Wassermann test, a faint trace of albumin in several preoperative specimens of urine, a phenolsulphonephthalein test of 57.2 per cent in two hours, a normal blood count and a basal metabolism of 126 per cent The electrocardiogram showed an absent "P" wave and arrhythmic ventricular contractions on June 15 He was given 15 minimis of digitalis three times a day, and on the nineteenth there was no pulse deficit On the twenty-first, a cardiogram still showed auricular fibrillation

Treatment and Course—Thyroidectomy was performed on June 22, most of the enlarged left lobe being removed A good operative recovery was made The specimen grossly was an adenoma with a small cyst Sections showed areas of closely crowded small follicles with no, or very little, colloid, lined with tall granular cells, others showed hyalinized connective tissue areas and areas with loose fibrous connective tissue with many vascular areas, diagnosis Adenoma

It is not quite clear from the history when the fibrillation ceased, but apparently very soon after operation A cardiogram on July 7 was normal, except for a slight negative deflection of the "T" wave On August 15, a note stated that the heart condition was excellent and that the patient had gained weight In October, he was still progressing favorably

CASE 3—*History*—A woman, aged 51, came to the hospital complaining of diarrhea and shortness of breath Her past history was negative, except for frequent attacks of diarrhea and a history of colitis ten years before, with which she was troubled for three or four years, and for which considerable silver nitrate was used in irrigations and in tablet form There was a history of an irregular heart and shortness of breath one year before Her family history was negative Her present illness began some time in August, 1923, when she became conscious of palpitation and a rapid heart and had diarrhea The previous winter she had been well and able to exercise strenuously With her rapid heart, in August she became short of breath This became so bad that in September she was put to bed and given digitalis, which resulted in so much improvement that she returned to her position as teacher The diarrhea began

again, her ankles began to swell, she was short of breath, and her heart became irregular.

Examination—On entrance to the hospital on October 7, physical examination revealed a nervous woman with marked exophthalmos. There was a definite bluish discoloration of the skin, more marked over the exposed surfaces. The skin was warm and moist, and the neck showed rather diffuse irregular enlargement over the thyroid region. The lungs were clear except for moist marginal râles. The heart action was tumultuous, irregular in force and rhythm, the rate 160 and the dulness increased transversely. The pulse rate was 120, with a deficit of 40. Abdominal examination was negative. There was some edema of the lower extremities, increased reflexes and marked tremor of the hands.

A fluoroscopic chest examination showed an irregular, enlarged heart, some cloudy lines running from the mediastinum and a high but movable right diaphragm. Laboratory tests revealed a negative Wassermann test and a trace of albumin in the urine. On October 10, the basal metabolism rate was 134 per cent, and a week later it was 126 per cent. Diagnosis then was exophthalmic goiter, auricular fibrillation and argyria.

Treatment and Course—In her progress it was noted that on rest in bed and administration of massive doses of digitalis her heart became slower and more regular, but the pulse by the end of the week, although there was less pulse deficit was still somewhat irregular at a rate of from 80 to 110.

The patient was operated on October 23. The specimen obtained showed definite exophthalmic goiter, except in one area in which the follicles were closely crowded, small, almost cordlike, with tall cells. In many areas the tall lining cells showed marked frayed free surfaces.

The day following operation the patient became restless, was semiconscious, had a rapid, weak pulse and rapid respirations with suppression of urine. She seemed to improve somewhat on normal saline given intravenously, but became worse in a short time. She was then given 5 per cent of glucose intravenously, which did not revive her from unconsciousness. The patient died that night.

Necropsy—This showed some broncho-pneumonia in the lower right lobe, a normal heart and fairly normal kidneys, except grossly very dark medullary pyramids. These and the skin sections showed a large amount of silver pigment.

Comment—This patient apparently had had one attack of auricular fibrillation one year before. The present attack of fibrillation began two months before entrance to the hospital but had been treated with digitalis, and she had improved enough to allow her to begin teaching school. Shortness of breath, irregular heart and diarrhea became so severe about one month before that she was put to bed and finally sent to the hospital. It is rather indefinite as to how long she had had goiter, and the exophthalmos, and a question whether colitis or diarrhea ten years before was not a part of the toxic goiter symptoms. It seems probable that the diarrhea present when she entered the hospital was due to the hyperthyroidism. Although she had apparently had one attack of auricular fibrillation, the last attack had become constant.

SUMMARY OF CASES

In the patients with goiter here then, we have had two women and one man, between 46 and 51 years of age. Two had adenoma, one exophthalmic goiter, one a paroxysmal, the other two, established fibrillation. The heart condition improved in all following the administration of digitalis—two receiving small doses, the last (exophthalmic) massive doses. The first two recovered completely from hyperthyroidism and the heart condition while one died following operation.

REVIEW OF THE LITERATURE

As has been demonstrated many times in various clinics, the heart condition can and does clear up with complete recovery of the patient. In a rather extended search of the older literature, we find that conditions as least similar to auricular fibrillation, if not true auricular fibrillation, were noted early. Germain Sée,⁷ in 1878 stated that rapid hearts in exophthalmic goiter are frequent, and he noted especially that arrhythmia had been overlooked by many. "Un autre phénomène qui accompagne les palpitations et qui a échappé à l'observation de la plupart des auteurs est l'arrythmie" (p 169). He believed this to be an important sign in goiter, that it often meant a valvular lesion, but also that it might indicate only functional disturbances. He noted an irregular interval between contractions, unequal force, and that the pulse rate (radial) was often slower than the heart rate, points which all prove, as well as can be done without a cardiogram, that he was dealing with a condition we now call auricular fibrillation.

The cases considered as auricular fibrillation are given in the table. The first one was reported by Griffith,⁸ who discussed the pulse rate and tracing, tumultuous heart action and low tension pulse. One of his patients, a woman, aged 35, had tumultuous heart action that improved markedly after administration of iron and digitalis. Whether this particular case was one of fibrillation is not clear, but we believe the two with irregular pulse tracings may be so considered.

Another case also not definitely one of auricular fibrillation was described by Fox.⁹ This occurred in a woman, aged 49, with attacks of rapid, irregular heart action lasting about a day. Gerhardt¹⁰ described a case of toxic goiter with a pulse of 100 or more and attacks in which the rate was from 120 to 200, definitely irregular and hardly palpable.

Marie¹¹ examined some patients particularly for heart irregularity, and found a normal regular pulse tracing. Kocher,¹² and Murray,¹³ in discussing cases of goiter, mentioned that some were found accom-

⁷ See, Germain Symptomes de la maladie de Basedow's, La France med 25 689, 1878

⁸ Griffith, A Hill Grave's Disease Analyses of Cases from Cliniques of Drs Little and Glascott, Tr Ophthal Soc of United Kingdom 6 60, 1886

⁹ Fox, H Brit M J 2 1184, 1890

¹⁰ Gerhardt, C Ueber krankhafte Pulsationen bei Schlussunfähigkeit der Aortenklappen und bei Basedow'scher Krankheit, Charité Ann 18 243, 1891

¹¹ Marie, P Contribution à l'étude et au diagnostic des formes frustes de la maladie de Basedow, These, Paris, 1893

¹² Kocher, A Ueber morbus Basedowii, Mitt a d Grenzgeb d Med u Chir 9 1, 1902

¹³ Murray, G R Exophthalmic Goitre and Its Treatment, Brit M J 2 1245, 1905

Cases of Atrial Fibrillation Reported in the Literature

Author	Year	Sex	Age	Pulse	Heart	Type of Fibrilla	Treatment	Result
Griffith and Foia	1886	F	35	133	Irregular, intermittent	Transient, 8 months	Ion and digitalis	20 months marked improvement, 3 years eyes well
Gerhardt	1890	F	49	Rapid	Irregular	Transient	Strophthalmic "no good"	Improved
Mosse	1891	F	32	120-200	Pulse, irregular	Evophthalmic	Recovered	
Sattler	1893	F	68	Irregular	Pulse, irregular	Evophthalmic	Improved, no attacks for two years	
Hossllin	1893	F	28	200	Pulse, irregular	Fevophthalmic	Bed rest, sedatives	
Bamberger	1910	M	31	240, 120-180	Pulse, irregular	Fevophthalmic	Operation	
Fahrenkamp	1914	F	41	180-200, 170-180	Tachycardia, pulse, irregular	Fevophthalmic	Digitalis, ligation, then operation	Still fibrillating
Krumbhaar	1918	F	56	170-180, 170-180	Pulse, irregular	Fevophthalmic	Attacks continued	
White and Lub	1918	F	39	Rapid, irregular	Rapid auricles, intermittent	Nodular goiter (adromic?)		
White and Morris	1918	F	56	Irregular ventriles	Toxic adenoma	Operation (?)	Normal heart	
Mason	1920	F	17	Fibrillation, mitral stenosis	Hypothyroidism	Digitalis	No fibrillation 1 month	
Orliss and associates	1922	F	17	Fibrillation	Fibrillation	Digitalis operation 20 days later	Fibrillation 9 days after digitalis, none 9 days after operation	
Schwenson	1922	M	49	Fibrillation, decompensated	Hyperthyroidism	Digitalis operation 20 days later	Fibrillation censed 2d day after digitalis	
Schoonmaker and Webb	1922	F	46	Fibrillation, decompensated	Dys	Golter		
Baumgartner, Webb and Schoonmaker	1923	F	51	Fibrillation	Fibrillation	Digitalis, Roentgen ray	Well for three years	
Hamilton	1922	6 cases	49	Permanent, 6 months, paroxysmal, 1 year	Toxic adenoma	Digitalis, Digitalis, operation	Aggravated for 5 weeks, no fibrillation later	
	12 cases			1 previous attack, now established, paroxysmal, weeks	Toxic adenoma	Digitalis, Digitalis, operation	No fibrillation after 5 weeks, nor since	
				"Established"	Hyperthyroidism	Digitalis, Digitalis, operation	Fibrillation after operation 1 day after operation	
				Weeks	Hyperthyroidism	Digitalis 4 and	No fibrillation after one, or both	
						operation 8	Fibrillation still prevent in 3	
							1 death, 3 no fibrillation, 1 fibrillating	

panied by irregular hearts. The latter stated that twelve were found in a series of 182 cases. Neither one gave any more definite statement, and in both the data was insufficient for diagnosing auricular fibrillation.

Mosse¹⁴ gave a more detailed description of the case of a woman, aged 68, with exophthalmos and definite toxic symptoms. The pulse was described as irregular and small, with irregular heart action over several years. He discussed the frequency of irregular heart action in goiter and stated that in 128 cases of exophthalmic goiter only this one was found.

Sattler¹⁵ described a case in a woman, aged 28, with definite symptoms of exophthalmic goiter and attacks of rapid irregular pulse. After rest in bed and sedatives she improved, but she had another attack three weeks later, then no more for two years, during which time her symptoms of goiter improved.

Hosslein¹⁶ noted marked attacks of palpitation, tachycardia up to 240, and irregular pulse in a woman with severe exophthalmic goiter seen in 1901. These attacks continued until operation in 1906. The pulse was later perfectly normal in rate and rhythm. He also referred briefly to another patient with struma who had severe attacks of tachycardia with absolute arrhythmia following treatment with iodin.

Bamberger,¹⁷ in discussing paroxysmal tachycardia in exophthalmic goiter, described three cases which were undoubtedly paroxysmal auricular fibrillation. One of these, in a man, aged 34, had attacks after administration of digitalis and after operation. In the other two cases, the treatment and result were not given. He said that the condition could not always be cured, and he noted that because of the irregular pulse these cases should not be classed with the usual paroxysmal tachycardias.

Fahrenkamp¹⁸ briefly described an irregular heart "arrhythmia perpetua" in various conditions. In four cases, one a case of exophthalmic goiter, he found an intermittent arrhythmia, with a rapidly beating auricle and an arrhythmic ventricle. The author does not use the term auricular fibrillation, although this term had been used by this time.

14 Mosse, M. Zur Kenntnis einiger seltener Störungen bei der Basedow'schen Krankheit, Berl. klin. Wochenschr. **44** 14, 1907.

15 Sattler, H. Die Basedow'sche Krankheit, Leipzig, 1909, 1910.

16 Hosslein, R. Die chirurgische Behandlung der Basedowschen Krankheit, Munchen Med. Wochenschr. **56** 105, 1909.

17 Bamberger. Paroxysmal Tachykardia bei Morbus Basedowii, Deutsch med. Wochenschr. **35** 1403, 1910.

18 Fahrenkamp, K. Vorübergehende komplexe Herzunregelmäßigkeiten unter den klinischen Bildern der Arrhythmia perpetua mit Beobachtungen über Vaguswirkung, Deutsch Arch. klin. Med. **117** 1, 1914-5.

Krumbhaar¹⁹ wrote on transient auricular fibrillation and stated that it occurred in infections, or toxic conditions, as hyperthyroidism. In another article,²⁰ he gives electrocardiograms taken in toxic goiters, and he briefly describes a few. One case is given in the table. In another case he mentioned (No. 10), the patient had had auricular fibrillation for ten years. Levine,²¹ in a series of fibrillation cases seen at Boston, briefly mentioned one case which occurred in hyperthyroidism.

Since that time there have been several articles on auricular fibrillation in goiter. One by White and Aub,²² was on electrocardiographic studies in thyroid disease. In forty-seven cases of hyperthyroidism, they found three patients with paroxysmal and three with permanent fibrillation—12.7 per cent. They give few details of individual cases. One patient with fibrillation and a pulse rate of 160 on December 20, was given digitalis, and on January 10 there was no fibrillation, and the pulse rate was 108. There was also no fibrillation when he was examined several months later. The first examination of a man on February 3 revealed a rapid pulse and no fibrillation, but this was present on February 16. Digitalis was given, but the patient still had fibrillation on February 25. Operation was performed on March 5, and the heart was normal when he was examined March 14 and on April 7.

White and Morris²³ in a paper on fibrillation incidentally mentioned thyroid conditions. One case of fibrillation cleared up the second day after digitalis therapy. In discussing transient or paroxysmal auricular fibrillation, Mason²⁴ gave these as occurring in 7 per cent of 250 cases of fibrillation. In one, exophthalmic goiter attacks of fibrillation had occurred for years.

The case reported by Crile and his associates⁴ is described in some detail. The patient had a toxic adenoma, was decompensated and fibrillating. She improved on digitalis therapy and other treatment, but she had four attacks the following year. She was then operated on and was well at the last report three years later.

In Hamilton's⁵ series of 200 goiter cases, eighteen showed fibrillation, of which six were paroxysmal at frequent intervals throughout

19 Krumbhaar, E. B. Transient Auricular Fibrillation, *Arch. Int. Med.* **18** 263 (Aug.) 1916.

20 Krumbhaar, E. B. Electrocardiographic Observations in Toxic Goitre, *Am. J. M. Sc.* **155** 175, 1918.

21 Levine, S. A. Auricular Fibrillation. Some Clinical Considerations, *Am. J. M. Sc.* **154** 43, 1917.

22 White, P. D., and Aub, J. C. Electrocardiogram in Thyroid Disease, *Arch. Int. Med.* **22** 766 (Dec.) 1918.

23 White, S. M., and Morris, R. E. The Eggleston Method of Administering Digitalis, *Arch. Int. Med.* **21** 740 (June) 1918.

24 Mason, V. R. Transient and Paroxysmal Auricular Fibrillation, *Bull. Johns Hopkins Hosp.* **31** 145, 1920.

months or years All of the patients were cured of hyperthyroidism by operation and had normal hearts afterward Digitalis had been used in these cases and some patients had shown normal hearts after its use before operation In twelve patients there was "established" fibrillation, of whom four received only digitalis, three of these continued to have fibrillation Of eight patients who had received digitalis and who had been operated on, four continued to have fibrillation

Schwenson²⁵ stated that according to the Scandinavian literature, fibrillation in exophthalmic goiter subsided after operation He reported a case which was aggravated at first by roentgen-ray treatment Later a normal electrocardiogram was obtained Kerr and Hensel²⁶ reported that auricular fibrillation and flutter occurred in one-third of 181 cases of goiter, of which 123 were adenoma and fifty-eight hyperplasia

The earliest mention of conditions which were probably auricular fibrillation in goiter was made by Germain See⁷ in 1878, who was struck by the fact that this irregularity of the heart had not been noted Several other writers described conditions which we believe were auricular fibrillation The first one given in our table (Griffith, 1886) possibly was not described in sufficient detail to be definitely classed as fibrillation The same may be said concerning the second case described in 1890 The other case, we believe, can be accepted as cases of fibrillation Bamberger, in 1910, gave definite descriptions of cases of paroxysmal fibrillation, and Krumbhaar, in 1918, first described the condition in this country At the end of the table is included a series of cases by Hamilton in which age and sex are not given

In analyzing the table we find that we have included twenty separate cases from 1886 to 1922, the sex was given in eighteen, and fifteen were females In fourteen, the age ranged from 28 to 68, nine were in the fourth and fifth decades, and in six the age was not stated The data bearing on fibrillation is given under pulses and heart columns for the earlier cases only After auricular fibrillation was known and the word used, proof has not been given in our table Fourteen of the patients had paroxysmal attacks, and only three had permanent fibrillation, while in five the data given was not sufficiently definite to justify the assignment of them to either class No definite data were given in some of the cases as to how long patients had had attacks or had had fibrillation The time mentioned varied from a few weeks to six years Our first patient, judging from her history, had had fibrillation for six months, the second patient had had intermittent attacks for one year, and the

25 Schwenson, C. Auricular Fibrillation in Hyperthyroidism, Ugesk f Laeger **84** 1756, 1922, abstr J A M A **80** 518, 1923

26 Kerr, W. J., and Hensel, G. C. Observations of the Cardiovascular System in Thyroid Diseases, Arch Int Med **31** 398 (March) 1923

third, with an attack one year before, had had constant fibrillation for two months Hoesslin and Bamberger's first patient had a history of attacks for from five to six years, but usually attacks had occurred only for several months or less before treatment was established.

As to the type of goiter in which fibrillations were described, in six the observers diagnosed exophthalmic goiter, and in five Basedow's disease, evidently, then, eleven cases of exophthalmic goiter in the eighteen cases. Probably five of the cases were toxic adenoma (one a nodular goiter), two were described as hyperthyroidism, one only as a goiter and one was not specified. In most of the cases it was not clear how long the patients had had goiters, nor how long these had given active symptoms. Our first and third patients had probably had goiter for ten years, with toxic symptoms at different times. The first had shown active symptoms for six months before entering the hospital, the second for one year, and the last, definite toxic symptoms for two months. Willius and Boothby³ stated that patients with exophthalmic goiter with constant fibrillation had had goiter for a longer time than those with intermittent or transient fibrillation and longer than any of those with adenoma with hyperthyroidism.

Griffith,⁸ using digitalis and iron, noted marked improvement, and stated that the eyes were normal three years later. Fibrillation ceased in two other cases after digitalis therapy. In six cases no treatment was recorded, in two of these frequent attacks of fibrillation continued, and the data were not definite in the remaining four cases. In Gerhardt's case strophanthus was said to have done no good, but the patient improved. The condition of the only patient treated with the roentgen ray was at first aggravated, but later fibrillation ceased. Sattler's patient improved on a treatment of bed rest and sedatives. Two patients continued to have fibrillation after administration of digitalis and operation, and three ceased to have fibrillation, one ceased to have fibrillation before operation. Two of our patients, one with constant fibrillation, and the other with intermittent fibrillation became well after digitalis therapy and operation. In two cases the patients are recorded as normal or recovered after operation alone.

White and Aub mentioned having had three cases of paroxysmal and three cases of permanent fibrillation, but they give the details in only one case, as shown in the table. In Hamilton's cases diagnosed as hyperthyroidism, there were twelve patients with "established" and six with paroxysmal auricular fibrillation. Some were relieved by digitalis alone, some by digitalis and operation. Seven of the patients with established fibrillation did not become normal after either method of treatment or after both. Willius and Boothby gave some detail in seven cases of exophthalmic and two of active adenomas. All received massive doses of digitalis, and six of the seven were operated on, although in

one only a ligation was performed. In this one patient decompensation later occurred again, the remaining ones recovered. Both patients with adenoma recovered after digitalis therapy and operation.

DISCUSSION

Although auricular fibrillation as such was not definitely described until 1907, cases almost like this, if not the same, were described as occurring in cases of goiter as early as 1878. Few definite details were given about specific cases until 1910, although cases which we believe to have been fibrillation have been described since 1886. There are more cases in which there are paroxysmal attacks of fibrillation, although Hamilton had twelve patients with established fibrillation in his series of eighteen cases. Patients with transient cases may have attacks lasting for from a few hours to a day or more, coming on in days or weeks, and in one case described the patient had been having attacks for six years. The fibrillation may persist for years, as in the case described by Mosse. Willius and Boothby, as some others, have distinguished between intermittent and transient fibrillation.

In the twenty cases, probably eleven can be considered as exophthalmic goiter. Hamilton's cases were called hyperthyroidism with no distinction between exophthalmic goiter or toxic adenoma. The earlier writers used the term Basedow and did not distinguish between types as is now done. There can be no question that all were active cases of goiter or hyperthyroidism. Willius at the Mayo clinic found fibrillation in a higher percentage in the cases of adenoma. Two of our cases were adenoma. Undoubtedly this condition occurs in a higher percentage among women than among men, although Germain Séé stated that arrhythmias were more frequent in males. Hamilton found that patients with a history of tonsil trouble or rheumatism were more likely to have fibrillation than were others. There is no evidence of this in the other cases reviewed in this paper. Hamilton also found that fibrillation was more likely to occur in older people, in patients twenty years older than the average age of patients with goiter. The majority of cases here reported occurred in persons in the fourth and fifth decades.

In many of the later cases the electrocardiogram has been used to diagnose or prove the fibrillation. In a few of the earlier ones, pulse tracings served to give a clear enough idea. The description of definite palpitation—rapid, irregular heart—in earlier cases was taken as evidence of fibrillation. It is rather strange that the condition was not noted earlier. However, despite the large percentages described by the Mayo and Boston clinics, smaller places either do not recognize the condition or it does not occur as often as these statistics show. The

condition has been diagnosed here three times in a clinic in which about fifty goiter operations are performed a year Undoubtedly the goiter cases have a toxic origin, but whether there is definite myocardial damage, as Mason stated, is questionable

As to prognosis, the results shown in the table would make one believe this good so far as the ultimate result is concerned since eleven of the eighteen patients were either relieved entirely or markedly improved in both thyroid and heart conditions Krumbhaar believed that an inverted "T" in the electrocardiogram was a bad prognostic sign Others have also suggested this, while Willius and Boothby wish to limit this to negative "T" in certain leads only In our first case there was a flat "T" wave in leads II and III about five weeks after operation, which became normal four months later, this one and the second case showed negative "T" in the same leads about three weeks after operation White and Aub believed that the heart conditions did not parallel the basal metabolism figures, a view apparently held by Willius and Boothby Our first patient here had a basal metabolism of 119 (by error this was reported as 199 per cent in the *Clifton Medical Bulletin*) and the others 126 and 134 per cent The latter patient, an exophthalmic case had a basal of 126 per cent one week after the first one In Hamilton's series patients with paroxysmal fibrillation have a better prognosis than those with established fibrillation In our first case, a patient with established fibrillation, the condition cleared up completely

Many cases have shown the value of digitalis therapy for fibrillation in goiter, as well as in other cases Kerr and Hensel stated that the dosage required is less than for those in which fibrillation is due to other conditions In two of our cases the condition cleared up on administration of only small amounts of digitalis and operation Some of the cases have cleared up, i e, fibrillation has ceased after digitalis alone In some fibrillation has continued until after operation In eight patients in this series who received digitalis or were operated on, or both, two continued to have fibrillation Three patients treated with digitalis alone recovered In Hamilton's series of four patients receiving digitalis, three continued to have fibrillation, and in eight patients with permanent fibrillation only three returned to normal, figures not as good as for the paroxysmal cases, since in fourteen cases here reported, nine cleared up complete and only in three did attacks of fibrillation continue Lahey, in discussing Tinker's²⁷ article, stated that 30 per cent if digitalized recover, with permanent cessation of fibrillation Our figures here show that a greater percentage than this recover

²⁷ Tinker, M B The Desperate Risk Goitre, J A M A **79** 1291 (Oct 14) 1921

SUMMARY

Germain Séé, in 1878, described irregular, rapid pulse and heart in cases of goiter in which there was probably fibrillation. Twenty cases, besides a series of eighteen by Hamilton, and figures from other clinics have been reviewed. Fibrillation may occur in hyperthyroidism, in both adenoma and exophthalmic cases, and may be paroxysmal or permanent for months or years. These patients should be given digitalis as other patients with fibrillation are given it, and operation should be performed even if there is fibrillation. We believe, as was stated in Schoonmaker and Webb's report, that the "gravity of the heart condition relative to thyroidectomy has been repeatedly overestimated, resulting in delay in operation and in a borderline dangerous myocardial insufficiency."

LESIONS DUE TO THE BITE OF THE
WHEEL-BUG *ARILUS CRISTATUS*
(HEMIPTERA; REDUVIIDAE)

MAURICE C HALL PH D

WASHINGTON D C

In the fall of 1922 my youngest daughter (M L H), aged 10 captured a wheel-bug *Arilus cristatus* (determined by W L McAtee) at Chevy Chase D C and was bitten twice by it on the inner aspect of the little finger of the right hand at a point near the nail. The finger became reddened and felt hot to the touch. In the course of a few days growths resembling papillomas developed at the sites of the punctures the largest of these projecting as a small hornlike structure. Both of these growths persisted for months, the largest slowly disappearing between six and nine months after the infliction of the bite. The injured finger remained warmer than the other fingers during this period and according to the patient's statement, still feels warmer than the other fingers a year later. The development of pronounced cutaneous growths after a bite appears indicative of the action of some toxin as a stimulant irritant.

Over thirty species of Heteroptera have been reported as attacking man. Of the genera reported in this connection from North America may be mentioned *Cimex Oropsocetes (Reduvius)* *Apiomerus Triphleps* *Arilus* (the species in question) *Conorhinus Rasahus Melanolcetes* and *Reduvius*.

Tissue growths such as 'galls' following injuries due to insects mites nematodes etc are not uncommon in plants. In animals tissue growths due to parasitic nematodes are not uncommon and in the case of one nematode *Gongylonema neoplasticum* infestations with the worm produce true malignant neoplasms with metastases in tissues other than those invaded by the worm. Tissue growths following the bites of insects appear to be uncommon in animals.

Some of the symptoms and lesions which have been reported in cases of persons bitten by so-called "kissing bugs" and related forms are as follows. The bite is followed by intense pain extending from the bitten finger to the head and followed by a feeling of faintness with recovery in less than half an hour except for slight local cellulitis (Herms), intense pain the swelling and irritation lasting for a week (LeConte quoted by Howard LeConte adds 'In very weak and irritable constitutions it may even prove fatal but it is not clear from the wording whether this statement refers to actual cases or to possibilities) a burning pain intense itching and much swelling with the appearance

of red blotches and welts all over the body and limbs, the effects lasting for months or disappearing in a few days (Marlatt), nausea, flushed face, palpitation of the heart, rapid breathing, rapid pulse, followed by profuse urticaria all over the body, the intensity of reaction varying with different individuals (Herms), appearance the day after the bite of a local cellulitis with a dark central spot, around which frequently appears a bulbous vesicle the size of a 10-cent piece and filled with a dark grumous fluid, followed by the formation of a small ulcer with a central necrotic area, the surrounding tissues more or less swollen and painful, and the swelling subsiding in a few days and followed by recovery in the course of a week (Davidson, quoted by Howard), pain, followed by numbness (Lintner, quoted by Howard), pain, followed by swelling, or swelling with but little pain (Howard), pain, rapidly increasing in severity and extending up the arm to the lower jaw, followed by slight swelling and no further inconvenience (Howard), serious illness, with recovery lasting almost a year (LeConte, quoted by Howard), inflammation with the arm almost useless for three days after the infliction of three bites (Osborn)

An inspection of the foregoing shows that the local reactions may include a sharp pain rapidly diminishing in intensity or rapidly increasing in intensity and extent, numbness, local inflammation lasting a short time or persisting for months, swelling which may be transient or persist for a week or longer, itching, vesicle formation, ulceration, necrosis and, in the present case, formation of tissue growths resembling papillomas, while the general reactions may include extension of pain from the finger to the head, faintness, generalized urticaria, which may be transient or may persist for a long period, nausea, flushed face, palpitation of the heart, rapid breathing, rapid pulse, vomiting or serious illness requiring almost a year for complete recovery

The case reported here was presented before the Entomological Society of Washington, and in the discussion Dr E A Schwartz and Mr A N Caudell stated that they had been bitten by *Arius cistatus* and that the bite was the most painful of injuries either of them had ever sustained from insects. In Mr Caudell's case, the bite was under the thumb nail and caused intense pain for an hour, and in both cases the unpleasant effects lasted for several days

A consideration of the fact presented here leads to the following theories as to the relationship between the bites of these bugs and the resulting symptoms and lesions. In some cases, the mechanical puncture and the injected toxin cause local pain, usually very severe, but sometimes comparable to that usually experienced from bee stings, and in such cases it might be assumed that the toxin injected was not very powerful or the patient actually or relatively tolerant of it, or that the

injection was subcutaneous but not intramuscular or directly into the blood vessels. In other cases, the bite causes severe systemic reactions, sometimes lasting for long periods, and in such cases it might be assumed that the toxin was very powerful or the patient distinctly intolerant of it, or that the injection was intramuscular or directly into the blood vessels. In this connection, it may be said that the long and powerful piercing beak of these bugs is capable of entering the relatively large and superficial veins of the hand and arm. In the case here reported, the development of papillomatous skin growths at the site of puncture might be referred to the stimulant irritant action of a toxin injected intradermally, giving rise to a pronounced local reaction with practically no systemic effects. The insect bit twice in rapid succession, causing pain of only moderate severity, not severe enough to discourage the patient in his attempt to capture the insect, and did not draw blood. While I have found no similar case in the literature, in a casual survey, it appears likely that a similar result would be produced under similar conditions, i.e., an intradermal injection of toxin in lieu of the usual deep puncture inflicted by the insect. That the bites of the large bugs are ordinarily deep enough to draw blood is evident from the fact that certain species of the genus *Triatoma* (*Lamius*) especially *T. megistus* are the carriers of the trypanosome causing Brazilian trypanosomiasis of man, Chagas' disease. The bites of these carriers, like those of the bed bug, are commonly much less painful than those of such bugs as the wheel-bug, which, as a rule, bite only when molested.

THE SKIN-REACTION TO MORPHIN

J D PILCHER, M D, AND TORALD SOLLMANN, M D
CLEVELAND

Solutions of morphin and its esters, when introduced into the skin, produce local reactions, consisting of the urticarial wheal with an erythematous areola (Sollmann and Pilcher¹) The lesions are quite like those formed in susceptible individuals by the local inoculation of foreign proteins, and in probably all individuals by inoculation of histamin or any one of a series of definite chemical substances (Sollmann²)

This local reaction to the morphins raised a number of interesting questions, some of which will be considered in this paper. Perhaps the most important of these concerns the possibility of the modification of the local reaction by habituation. Does the high degree of tolerance to the toxic actions of the morphins that is acquired by addicts extend also to the local reactions? Or, stated conversely, does the local reaction vary with changes in the systemic susceptibility, as is the case with desensitization or "habituation" to the protein poisons? The answer to this question is not only of scientific interest, but if it were to be positive, it might have a great practical value for the diagnosis of opiate addiction. Unfortunately, from this point of view, the answer is in the negative. The local reaction is not at all modified by the acquirement of the systemic tolerance; it is the same in patients during the various stages of habituation and dishabituation, as it is in normal individuals. Scientifically, this result is of interest in confirming the fact that the acquired tolerance does not extend to all the effects of morphin, but that it is confined to certain functions.

As regards central actions, Van Egmond³ found that tolerance was acquired in the order of pupils > emesis > defecation > narcosis > respiratory center, while no tolerance was acquired toward the central vagus action. Langer⁴ also failed to produce any tolerance to the convulsant action of diacetylmorphin. Apparently, the tolerance involves only the psychical inertia and its secondary results, among which should probably be included the miosis, the constipation, and the respiratory depression that is the immediate cause of the fatality. It is natural

* From the Department of Pharmacology, Western Reserve University School of Medicine

1 Sollmann, Torald, and Pilcher, J D J Pharm & Exper Therap 9 309 (March) 1917

2 Sollmann, Torald Jour Pharm & Exper Therap 9 391 (April) 1917

3 Van Egmond, A A G Arch Exper Pathol & Pharm 65 197, 1911

4 Langer Biochem Ztschr 45 221, 239, 1912

to conceive that this psychical inertia could be compensated relatively simply by the gradual education of psychic adjustments. The acquired tolerance to the emetic action could also be explained on a psychic basis. The vagus and convulsive centers and the local inflammatory actions lie entirely outside of the psychic sphere and therefore, could not be corrected by psychic compensations.

It may be added that it is also impossible to desensitize locally to morphin or histamin by repeating the applications at ten minute intervals (Sollmann⁵), a method that desensitizes the *specific* hypersusceptibility of the protein of foods etc (Mackenzie and Baldwin⁶)

When the morphin skin-test is made by intracutaneous injections as will be described the response is remarkably uniform in the great majority of subjects, normal or addicts. No significant differences are found between males and females or between the white and colored races. A few individuals gave a moderately exaggerated reaction but these also gave a similarly exaggerated reaction to the control injection of physiologic sodium chlorid solution i.e. their skin was hypersensitive to irritation in general and not especially to the morphin irritation. It is probable that patients with a true 'idiosyncrasy' toward morphin show a highly exaggerated and specific reaction but none of these came under observation.

On the other hand preexistent edema of the skin masks the reaction to morphin, so that the latter may perhaps even serve as a test for the existence of edema or indeed generally for the condition of the skin, its delicacy and irritability.

METHODS

The intradermal method was used in preference to the scratch methods, since the former not only acts with much smaller concentrations but also permits a much better control of the quantity of solution introduced into the skin and therefore gives more uniform results. The injections were made into the cutis of the flexor surface of the forearm, a sufficient quantity of the solution being introduced to produce an immediate distention wheal about 5 mm in diameter. A control wheal was made with physiologic sodium chlorid solution containing 0.25 per cent of tricresol and the course of this was compared with that of strictly similar wheals produced by the solution with the addition of morphin hydrochlorid, in the proportions of 1:1000, 1:100,000 and 1:1,000,000. The latter solution gave either no reactions beyond that of the saline control or only a minimal increase. The

5 Sollmann, T. J. Pharm & Exper Therap 9:147 (Jan) 1917

6 Mackenzie, G. M. and Baldwin L. B. Local Desensitization in Hypersensitive Individuals and Its Bearing on Prevention of Hay-Fever (Arch Int Med 28:722 (Dec) 1921)

1 100,000 solution always gave mildly positive reactions. With the 1 1,000 the response was always so marked that it was deemed superfluous to employ more concentrated solutions. This illustrates the lower sensitiveness of the scratch method, which gives at most slight reactions with the 1 1,000 solutions. A number of experiments were also made with a 1 10,000 solution, but as this gave no additional information, its use was discontinued. The total quantity of morphin introduced at a complete test, comprising three injections, is about 0.1 mg (1/600 gram), so that there is no possibility of any perceptible systemic effect whatever, nor was any such effect ever noticed by either normal subjects, addicts, or exaddicts.

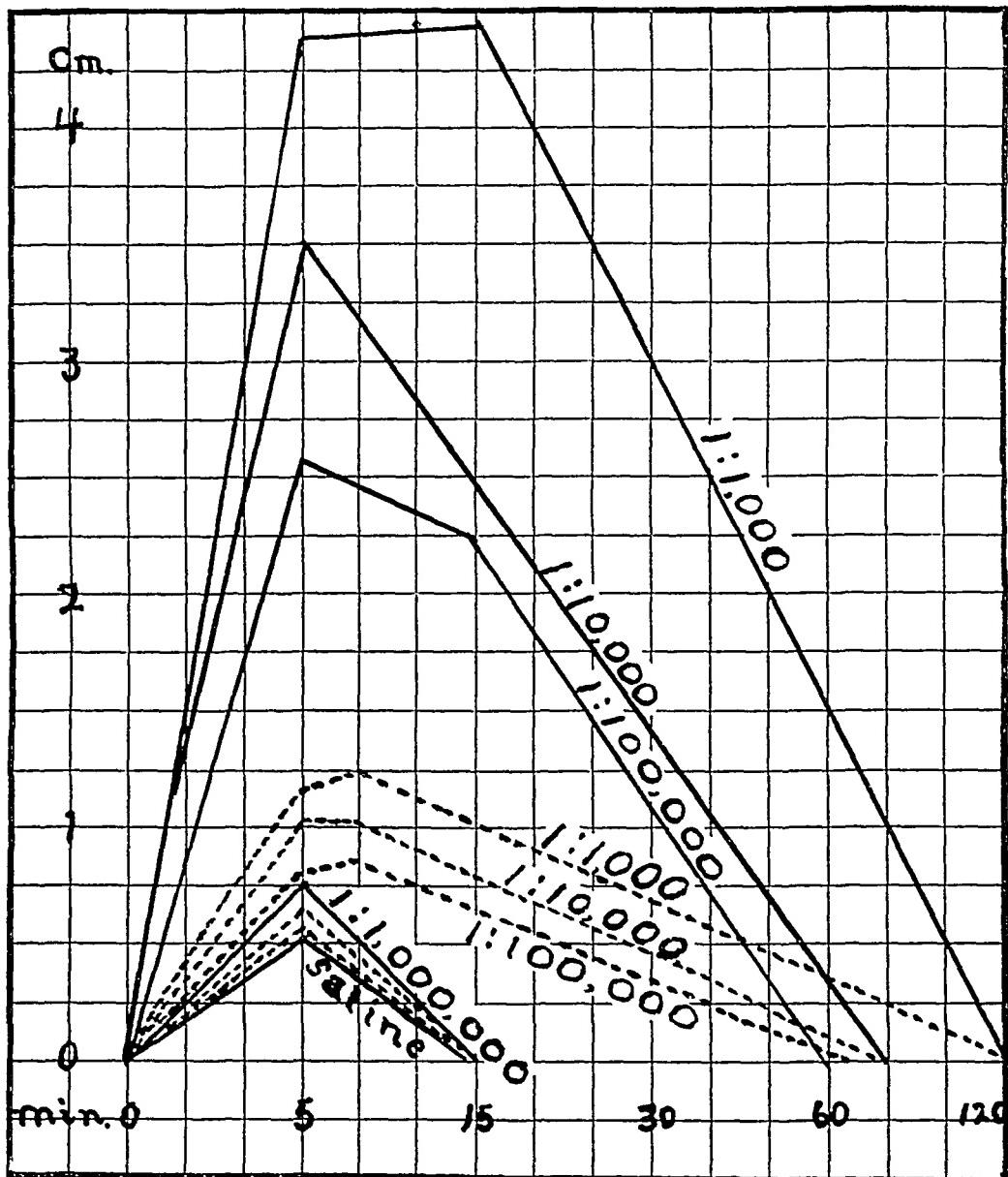
OBSLRVATIONS

The injection sites were usually observed at five, fifteen, thirty, sixty and 120 minute intervals following the injection, the size of the wheal and of the erythematous area being measured. As the reactions subside, the outlines of the wheals and, to a less extent, of the areola become less and less distinct, so that accurate measurements are impossible. The reactions were then recorded as "fading" or "faded."

Normal Course of the Morphin Reactions—As has been stated, this is remarkably uniform, although minor quantitative variations are found, even in the same individual, for one thing, because it is not practical to introduce exactly the same quantity of the solution into the same area of skin. These accidental variations may be smoothed out by multiplying the observations, and since the conditions observed by us did not modify the course of the reactions, we may employ the medians of the entire series of about eighty subjects as a basis for the "normal course." The phenomena are most typical when they are most marked, i.e., with the 1 1,000 solutions.

Course of the Reaction to the 1 1,000 Solution—There is a momentary stinging sensation, but exceptionally a little pain. Then the primary 5 mm wheal, produced mechanically by the intracutaneous injection, becomes rapidly reddened, increases in size and is surrounded by a congested area of rather irregular outline. The maximum intensity is reached in from five to ten minutes, seldom later. The wheal is then about 12 mm in diameter, somewhat doughy, moderately raised above the surrounding skin, rather sharply circumscribed and fairly circular, but sometimes having a few pseudopods. It is surrounded by an erythematous areola having the diameter of from 4 to 6 cm bright or "angry" red near the wheal, paler and somewhat mottled toward the periphery. Usually the size of the wheal and the congested area were roughly proportional, i.e., the larger the wheal, the larger the congested area. There were exceptions, as illustrated by two experiments with

the 1:1,000 solution. One subject, aged 55 had a wheal 1.6 cm and a congested area 4 cm in diameter, while a second subject, aged 23, had a wheal 1 cm and a congested area 6.8 cm in diameter. This variation is probably due to want of parallelism between the permeability and dilatation of the skin capillaries.



Course of morphin (composite of all experiments). The curves represent the median diameter of the wheals (broken line) and areolas (solid line). The diameter is given in centimeters, the time after injection in minutes.

Subsequent Course.—Usually within fifteen minutes after the injections, the phenomena begins to subside. The wheal becomes flatter and paler, and its borders are less distinct. The areola decreases in size and color. The fading progresses rather slowly. In an hour after

the injection, the areola is quite faint, and the site of the wheal pale, and still indurated, but not elevated above the surrounding skin. Some-what later, one and one-half or at most two hours after the injection, all visible trace of the reaction has disappeared.

Reactions to the More Dilute Solutions—These differ from those just described merely in intensity and duration, these two being fairly parallel. Their course is shown graphically in the accompanying figure.

Morphin Addicts Examined—The addicts used in this study included a small group who were receiving known quantities of morphin from the Narcotic Bureau, and a larger group of inmates of the "House of Correction" undergoing the treatment by rapid withdrawal of the drug. There is no doubt that all the subjects of both groups were confirmed addicts, with considerable tolerance. All but two (and these had been receiving known quantities from the Narcotic Bureau) bore the scars of hypodermic punctures, and with few exceptions, the scarring was quite extensive. All except these two stated that they took their drug hypodermically, a very few by severely scratching the skin and rubbing the alkaloid into the wound. The conditions were therefore optimal for acquiring not only a systemic but also a local tolerance to the morphin.

A record was kept of the statements of the subjects as to the duration of their addiction and their normal dosage. The majority claimed that they had taken the drugs for many years, the average being at least ten years, with extremes of from a few months to forty-one years. Many were physically much below normal. Those who had been without the drugs for some weeks were usually in excellent physical condition. Their ages ranged from twenty to seventy-four years. The mean of the claimed daily dosage was between 10 and 15 grains (0.65 and about 1.00 gm.) of morphin or "heroin" (diacetylmorphin), with extremes of from 5 to 90 grains (0.32 to 5.85 gm.). The addicts were generally very willing to furnish these data, but as they may be easily influenced by the hope of securing a larger supply or slower withdrawal little use was made of their direct statements. Other evidence is adequate to establish their tolerance. Those supplied by the Narcotic Bureau received from 3 to 5½ grains (0.19 to 0.35 gm.) of morphin sulphate daily from that source. Many others had received a controlled dose before their admission to the House of Correction, and their tolerance was manifest from the degree of their response.

Classification of the Subjects—In view of the unreliability of the exact degree of habituation, it seems scarcely worth while to classify the subjects from that point of view. The arrangement actually adopted accords with the stage of the treatment.

Group A. Current addition: Five subjects who were receiving from 3 to 5½ grains of morphin a day from the Narcotic Bureau

Group B: Abstinence symptoms Eighteen subjects still receiving morphin or diacetylmorphin in reduced but still large dosage (usually from 1 to 4 grains (0.065 to 0.260 gm) on the day preceding the test) and showing abstinence symptoms slight in about two-thirds of the patients severe in the others

Group C. Complete withdrawal (short i.e. of from ten to twelve days) Ten subjects Abstinence symptoms had completely disappeared

Group D. Complete withdrawal (intermediate i.e. of from two to ten weeks). Nine subjects

Group E. Complete withdrawal (long i.e. of from six to seven months) Nine subjects

TABLE 1.—Comparative of *L. terebrare* Merck Test in Addicts and Nonaddicts*

	Morphin Hydrochloride 1/1000				Morphin Hydrochloride 1/10,000				Morphin Hydrochloride 1/100,000			
	Wheal		Areola		Wheal		Areola		Wheal		Areola	
	5	30	5	30	5	30	5	30	5	30	5	30
<i>Nonaddicts</i>												
Group I—Normal	12	—	—	—	—	—	—	—	—	—	—	—
Group II—Therapeutic addicts	—	F	—	F	—	F	—	F	—	—	—	—
Group A—Current addicts	12	F	4	F	10	7	3	F	—	C	—	F
Group B—Abstinence symptoms	12	F	4	F	8	F	16	F	—	C	—	C
<i>Addicts</i>												
Group C—10 to 12 days	11.5	F	4	F	8	F	17	C	—	C	—	C
Group D—2 to 1 week	12	—	5	—	8	—	17	—	C	—	C	—
Group E—6 to 7 months	12	F	7	—	8	F	15	F	8	C	—	C
Group F—Average of all groups	12	F	4	F	8	F	17	F	—	C	—	C

* The numbers correspond to the mean diameter in millimeters of the wheal or areola in each exudate and nonexudate. F indicates that the response has faded materially so that it is impossible precisely to completely — indicates a positive reaction but too faint for measurement.

For comparison with these we have two groups of nonaddicts

Group I normal Seventeen normal individuals who had never used opiates habitually, and many of whom had never received effective doses even therapeutically

Group II therapeutic. Four subjects who had never been addicted to opiates but who for therapeutic purposes had received several small doses in the hospital on the days preceding the test

The comparative results as to intensity and duration of the reaction may be illustrated by the observations for from five to thirty minutes after injection as shown in Table 1. The data for all the other periods have been similarly tabulated but need not be reproduced as they merely confirm the conclusions in Table 1.

A glance at the table shows the identity of the figures in each vertical column, i.e., the identity of the reaction of all the groups, as concerns the maximal or the minimal concentrations, or the intensity or duration of the response.

Table 2 illustrates that the extremes, as well as the medians, are uninfluenced by habituation.

TABLE 2—*Extreme Variations of the Morphin Reactions**

	Wheals 11-18	Areola 20-65
Nonaddicts		
Addicts		
Group A	14-14	30-45
Group B	9-20	14-60
Exaddicts		
Group C	10-18	30-60
Group D	10-20	40-60
Group E	9-13	65-67

* Measurements (mm) 15 minutes after injection of 1:1000 solution. The lettering of the groups is as in Table 1.

COMPARISON OF THE MORPHIN TEST OF WHITE AND COLORED RACES

Whether the greater resistance of the negro-skin to certain irritants, such as light, and dichlorodiethylsulphide, extends also to morphin seemed worth investigating. We utilized thirteen negroes of light to very dark skins belonging to various addiction groups, but as we have shown that addiction does not alter the response, they may all be grouped together. The results are shown numerically in Table 3. Only the numbers for the wheals of the five-minute period are reproduced.

The wheal response is evidently identical. The color of the areola cannot be differentiated sharply from the dark color of the surrounding

TABLE 3—*Median Diameter (Mm) of Wheal After 5 Min*

	Morphin Hydrochlorid		
	1 1000	1 100 000	1 1,000 000
White	12	8	0
Colored	12	9	0+
General average	12	8	+

normal skin of the negro, although it can be seen somewhat dimly. In the lighter mulattoes, the reaction is sufficiently visible for measurement, and then averages the same as in the white race.

INFLUENCE OF SEX

The results in thirty-nine males and nineteen females were tabulated and found to be almost identical. Actual figures show a somewhat smaller wheal and a somewhat larger areola in females. For instance, five minutes after the injection of the 1:1000 solution, the wheals

average 12 mm in the males, 11.5 in the females, the areolae, 40 mm in the males, 45 in the females. These differences are within the range of statistical variations. They might, however, represent a true difference in reaction, due to differences in the structure of the skin or the responsiveness of the capillaries to irritation. We have the impression that fine or delicate skins, regardless of sex, gave a greater reaction than thick, dense skin. A majority of the subjects that gave reactions above the average were noted as having fair skins but exceptions to this were numerous.

Age has no apparent influence in the morphin response.

THE EFFECT OF EDEMA

The test was applied to three subjects, not addicts, who had edemas secondary to cardiac insufficiency, their edema varying from slight to an extreme degree. In these subjects the reaction was distinctly less than in the normal individual, as to both the size of the wheal and of the congested area, and the rate of disappearance. The greater the edema the less was the reaction. With slight edema, the reaction was similar to the normal, but persisted for a shorter time, with moderate edema, the injection wheal formed, increased but little in size and soon faded, with edema so extreme that fluid oozed from the needle puncture, no wheal could be formed even with a 1 per cent morphin solution. The erythematous area was slight in one case and could not be seen in a second as the subject was a negress. In the subject with extreme edema, an approximately normal congested area was present, which was of somewhat lesser duration, and no increase in congestion was noted with the 1 per cent solution. The diminished response in the presence of the edema might be due to the rapid dilution or dispersion of the solution. It is more likely that a tissue already edematous cannot swell much more, and capillaries that are compressed by edema cannot dilate effectively.⁷

In any case, the edema must be actually present if it is to check the morphin reaction, for practically normal wheals and areolas were obtained on two boys, one with severe chronic nephritis and the other with cardiac insufficiency (aortic insufficiency and myocarditis), who were not edematous at the time, although each had been so formerly.

CONCLUSIONS

1. Morphin administered intradermally produces a wheal surrounded by a congested area, the reaction increasing in intensity and duration.

⁷ Since the foregoing was written we note that W. B. McClure and C. A. Aldrich (*Time Required for Disappearance of Intradermally Injected Salt Solution*, J. A. M. A. 81:293 [July 21] 1923) recently described a similar phenomenon, edema hastening the rate of disappearance of the induration produced by the intradermic injection physiologic sodium chlorid solution.

with the concentration. The minimum concentration of 1:1,000,000 was effective in about one half the experiments. A 1:100,000 solution always produces a wheal and congested area.

2. The reaction reaches the maximum in from five to fifteen minutes and disappears in from one to two hours.

3. The reaction is in every respect the same in addicts and in normal individuals. Systemic tolerance of morphin, therefore, does not induce local (skin) tolerance.

4. The reaction is identical in the young and in old adults, in males and females, in the white and negro races.

5. The reaction is probably somewhat more marked in skins of fine texture.

6. The presence of edema greatly lessens the wheal formation, and in extreme cases of edema, abolishes it.

THE P_H AND BUFFER VALUES OF DUODENAL CONTENTS DERIVED FROM NORMAL MEN*

C. W. MCCLURE, M.D., O. C. MONTAGUE

AND

L. L. CAMPBELL, PH.D.

BOSTON

The present communication reports the results obtained from a study of P_H and buffer values the latter determined by electrometric titration of duodenal contents derived from normal persons.

With the exception of the comparatively recent publications of McClerden¹ and of McClure² and their co-workers there are no reported studies of the p_H of duodenal contents collected during the period when intestinal digestion was definitely known to be in progress. The paucity of observations of this nature led us to make a somewhat more comprehensive study of the subject.

EXPERIMENTAL PROCEDURE

For the purposes of the recent investigation, duodenal contents were obtained from normal young men. The duodenal tube was taken before breakfast, fifteen hours after the last food intake and nine hours after the last drink of water. The tip of the tube was allowed to pass into the proximal end of the second portion of the duodenum, a distance of from 5 to 10 cm. from the pyloric sphincter, the position being determined by fluoroscopy. The subject then ate a meal consisting of either a pure protein (edestin), a pure fat (olive oil), a pure carbohydrate (arrowroot starch), or a mixture of these substances. Before ingestion, the edestin was thoroughly moistened with water, and the arrowroot starch was cooked in boiling water until a thick gelatinous translucent mass was obtained. Twenty-five grams of each substance constituted a meal, and in order to make the desired volume 25 c.c. of water was shaken with the olive oil just prior to its ingestion. The meal composed of a mixture of the three food substances contained 8.33 gm. of each of them. After the ingestion of a meal the subject reclined on the right side and duodenal contents were collected by siphonage over the

* From the Evans Memorial and the Department of Physics, Simmons College.

¹ McClerden, J. F.: Bassell, F. S., Lowe, E. R., and Meyer, P. F.: Hydrogen-Ion Concentration of Contents of Small Intestine J. A. M. A. 75:1638 (Dec. 11) 1925.

² McClure, C. W., Wetmore, A. S., and Reynolds, L.: Physical Characters and Enzymatic Activities of Duodenal Contents: Findings During Gastric Digestion in Normal Young Men. J. A. M. A. 77:1468 (Nov. 5) 1921.

following periods (1) from the time of ingestion of food up to the abrupt appearance of very dark colored bile, (2) over the succeeding period of thirty minutes, and (3) over a second half-hour period. During the first period of collection, intestinal digestion was at its minimum, while during the second and third periods, intestinal digestion was in its normal degree of activity. In certain experiments, duodenal contents were collected before the ingestion of food. In other experiments, collections were made over two successive thirty-minute periods after the ingestion of 50 c.c. of tap water. All duodenal contents were collected in flasks immersed in ice water.

The apparatus employed in the determination of the p_H of duodenal contents consisted of a Leeds and Northrup potentiometer, a D'Arsoval galvanometer, a standard Eppley cell, a calomel half-cell, a hydrogen electrode and a special titration vessel of the conical Bovie type. Into this vessel were inserted the hydrogen electrode, the capillary tube from the calomel cell and a thermometer. The advantage of the conical cell is that the material in it may be thoroughly mixed by the inflow of hydrogen.

The hydrogen electrode consisted of a straight glass tube in which was sealed a fairly large, straight platinum wire that projected about 1.5 cm. from the sealed end of the glass tube. This tube was inserted in the hydrogen delivery tube so that the inflow of hydrogen completely bathed the platinized end of the wire. The wire was platinized in a 5 per cent solution of platinic chloride, thoroughly washed and hydrogenized in a solution of sulphuric acid and then washed free from acid.

The calomel half-cell was constructed in accordance with the usual standard specifications. The end of the potassium chloride capillary tube leading from the calomel cell and entering the titration vessel was drawn down to a smaller diameter and bent into a J shape. This caused the lower, open end to point upward in the titration vessel, which minimized convection and diffusion of liquids in the tube and vessel.

The reliability of the apparatus was frequently tested by measuring the electromotive force between the calomel cell and the hydrogen electrode in a solution of hydrochloric acid of known normality and p_H . During all determinations, there was no evidence of the electrode being "poisoned."

The p_H of the duodenal contents was determined shortly after the duodenal contents were collected, and at room temperature in the neighborhood of 20 C. Between determinations, the contents were kept in a refrigerator at ice temperature.

The buffer values of the duodenal contents were determined by titrating 50 c.c. of the contents with tenth normal hydrochloric acid or

sodium hydroxid solution, according to whether the original material was alkaline or acid. The resulting p_H values were determined up to and beyond the neutral point. Curves of these values were plotted against the amount of acid or alkali, and the amounts needed to bring the p_H values to 7 were read from the curves.

The buffer values of the duodenal contents were computed from the equation developed by Van Slyke³

$$\beta = \frac{\Delta \beta \text{ or } \Delta A}{\Delta p_H}$$

ΔB , or ΔA , is the amount of tenth normal alkali or acid solution required to neutralize 1 cc of duodenal contents, or ΔB , or ΔA , $= \frac{V \cdot N}{V}$ in which V is the volume of the alkali or acid used, N the normality of the solution and V the total volume of the original duodenal contents in the titration vessel. The total change in the p_H value from the original to the neutral state is Δp_H .

The β values in the tables of the present report are average values, since the amount of acid or alkali required to effect a change in the p_H value by 1 varies for different H-ion concentrations in the same material. The buffer value of a given specimen of duodenal contents was estimated from the foregoing equation only when the titration curves of the p_H change against the amounts of alkali or acid added formed fairly straight lines.

EXPERIMENTAL DATA

The p_H was determined in fasting duodenal contents and in those collected after the ingestion of 50 cc of tap water. The collections were divided in periods of thirty minutes each. The term fasting duodenal contents designates the contents of the duodenum about fifteen hours after the last food intake and nine hours after the last drink of water. But in taking the tube, subjects swallow much saliva. It is also well known that the normal fasting stomach contains more or less acid secretion, cellular debris and mucus. Undoubtedly, the stomach throws these materials over into the duodenum, so that there was not a truly fasting state of the stomach during the course of the experiments reported here. Previous work has shown that the concentrations of pancreatic enzymes and of bile in duodenal contents are the same in contents obtained after water drinking as in those removed from the "fasting" duodenum. The results of the present study are outlined in Table 1.

A perusal of Table 1 shows that the p_H of the duodenal contents of a fasting subject was either above or below 7, while that of those derived from water were above 7. These duodenal contents were all pale yellow and of slight viscosity.

³ Van Slyke, D. D. J. Biol. Chem. **52** 525 (June) 1922.

The p_H of duodenal contents was determined in those collected from immediately after the ingestion of food up to the time of the abrupt change from pale yellow to a very dark color occurred. During this period, no stimulating effect of the ingestion of food on the flow of bile or pancreatic juice had yet occurred. The results are outlined in Table 2, which shows that the p_H of duodenal contents collected under the conditions described may be either above or below 7. These contents were all light yellow and of slight viscosity. The duration of the

TABLE 1.— P_H and Buffer Values of Duodenal Contents Collected Over 30-Minute Periods, Either While the Stomach was Fasting or After the Ingestion of 50 cc of Tap Water

Subject	p_H	Buffer Values				State of the Stomach
		No of Cc N/10 HCl or NaOH to Bring 1,000 Cc Duodenal Contents to p_H 7	β (buffer) Values No of Cc N/10 HCl or NaOH to Change p_H Value	1,000 Cc Duodenal Contents by Unity	1,000 Cc Duodenal Contents by Unity	
		180	167	167	167	
B	8.075					Fasting
C	6.727					Fasting
I	8.264					50 cc tap water ingested
A	7.579					Fasting
	7.588					1st 30 minutes after water ingestion
	8.003					2d 30 minutes after water ingestion

TABLE 2.— P_H and Buffer Values of Duodenal Contents Collected from Immediately After the Ingestion of Food up to the Onset of Intestinal Digestion

Subject	p_H	Buffer Values				Kind of Food Ingested
		No of Cc N/10 HCl or NaOH to Bring 1,000 Cc Duodenal Contents to p_H 7	β (buffer) Values No of Cc N/10 HCl or NaOH to Change p_H Value	1,000 Cc Duodenal Contents by Unity	1,000 Cc Duodenal Contents by Unity	
		110	144	144	144	
B	6.240					Olive oil
	7.811	180	222	222	222	1 destin
C	6.937					Olive oil
	7.485	98	202	202	202	1 destin
	5.961					Olive oil, edestin and arrowroot starch

periods of collection varied from eight to thirty-nine minutes. During the collection of these specimens, food appeared in them within the first few minutes.

Tables 1 and 2 deal with duodenal contents collected over periods during which the stimulating effect of food on the flow of bile and pancreatic juice was not present,⁴ as will be discussed later. Table 3 presents the results obtained from a study of the p_H and buffer values of duodenal contents collected during periods when the stimulating effect of food on the flow of pancreatic juice and bile was present, as will also be discussed later.⁴ This effect began with the change from

⁴ McClure, C. W. and Wetmore, A. S. Boston M & S J 187 882 (Dec 14) 1922

the initially light yellow colored bile to a very deep colored bile. The findings in these duodenal contents are outlined in Table 3, a study of which shows that in both subjects duodenal contents derived after the ingestion of either olive oil or arrowroot starch were alkaline (p_H above 7), while those collected after ingestion of edestin or the mixture of food substances were acid (p_H below 7). These duodenal contents were all some shade of dark yellow and of moderate viscosity, and all contained food.

The figures for buffer values which are presented in the tables, with their significance and also that of the p_H values will be discussed under separate headings.

TABLE 3.— p_H and Buffer Values of Duodenal Contents Collected Over Two Consecutive 30-Minute Periods After the Onset of Intestinal Digestion

Subject	p_H	Buffer Values				Kind of Food Ingested	
		No. of Cc N/10 HCl or NaOH to Bring 1,000 Cc Duodenal Contents to p_H 7	β (buffer) Values	No. of Cc N/10 HCl or NaOH to Change p_H Value 1,000 Cc Duodenal Contents by Unity	Change p_H Value		
B	7.163	26	159			Olive oil	
	8.102	169	153				
	5.101	324	172			Edestin	
	3.172	710	185				
	7.013						
	7.971	223	230			Arrowroot starch	
	6.806	76	392			Olive oil edestin and arrowroot starch	
C	6.879						
	7.011					Olive oil	
	6.743	36	140			Edestin	
	6.684	66	209				
	7.178					Arrowroot starch	
	7.745	91	122				
	6.367	174	275			Olive oil edestin and arrowroot starch	
	6.000	20	250				

BUFFER VALUES

Enzyme action is profoundly affected by the hydrogen-ion concentration of the medium in which the active principle is either suspended or dissolved, and the maintenance of the p_H value of the medium is conditioned in large measure by the concentration and efficiency of the buffer substances present. Buffer conditions are included in the present report as a part of the examination of the duodenal contents, and the values obtained are collated in Tables 1, 2 and 3.

Some years ago, Van Slyke³ published an interesting generalization in which he defined as the buffer value β the relationship of the amount of acid respectively alkali necessary to produce a change of 1 in the value of the p_H . The equation developed by Van Slyke has already been described in this article. An inspection of the conditions shows that at best this buffer value as computed for duodenal contents would

be only an approximation of an empiric relationship, and in the extreme cases could range from limits of zero to infinity in magnitude.

In the present study, the titrable acidity or alkalinity has been determined by bringing a definite quantity of the duodenal contents to the neutral point by the addition of standard acid or alkali, the choice governed by the initial reaction of the duodenal contents, p_H values were determined initially and the neutral point evaluated by further potentiometric comparisons, after addition of successive portions of the titration solutions. By dividing the number of cubic centimeters of the titration fluid with the numerical expression of the p_H range involved in the titration, an empiric value has been derived somewhat analogous to the β value of Van Slyke.

When calculated on the basis of a change of one in the value of the p_H , the buffer values for duodenal contents are surprisingly uniform (Tables 1, 2 and 3), there being evidences of an almost linear relationship.

The presence of olive oil would not influence the titration value of duodenal contents on addition of a solution of hydrochloric acid. The amounts of either edestin or arrowroot starch which were grossly visible in duodenal contents were minute, as were, also, the quantities of non-protein nitrogen or of sugars, as determined by analysis. For these reasons, the buffer values were slightly, if at all, influenced by the content of food substances.

The absence of buffer action of the food substances used and the uniformity found in the buffer values of the duodenal contents indicate that the physical chemical factors governing the buffer conditions were approximately the same in all specimens of duodenal contents, i.e., the findings indicate that the various types of food substances had about the same stimulating effect on the external functions of the liver and pancreas as regards the production of buffer substances.

HYDROGEN-ION CONCENTRATION

In a former publication⁴ it was shown that whenever food reaches the duodenum, there eventually occurs coincident augmentation in the flow of bile and pancreatic juice, i.e., food in some way produces a coincident stimulation of the external functions of the liver and pancreas. Since that publication appeared, the coincidence of this dual stimulation has been confirmed by the application of newly devised methods,⁵ which furnish an index to the concentration of the bile present in duodenal contents. From these studies, it is concluded that in normal man the production of a materially augmented flow of bile is accompanied by stimulation of the external secretory function of the pancreas.

5 Unpublished observations

The increase in flow of bile is readily detected on gross inspection, and occurs when the initially light colored duodenal contents abruptly change to a very dark shade of yellow. Thus, this color change inferentially furnishes an accurate index to the time when the onset of stimulation of the flow of pancreatic juice occurs in normal persons.

In the same publication¹ it was demonstrated that after pancreatic stimulation had occurred, it continued as long as food was passing through the duodenum. In former studies⁶ it was shown that meals of a volume of 50 cc produce the same degrees of pancreatic, and apparently hepatic, stimulation as do meals of a volume of 300 cc.

The foregoing discussion permits the conclusion that the duodenal contents analyzed in Table 3 were collected while the external functions of the liver and pancreas were as active as is usual during normal intestinal digestion. It will be recalled that these duodenal contents were collected over two consecutive thirty-minute periods after the abrupt change to dark colored bile occurred, following the ingestion of food. Table 3 shows that during the periods of collection the duodenal contents derived from edestin and the mixture of foodstuffs were acid, while those from olive oil and arrowroot starch were alkaline. Evidence has been presented⁴ showing that olive oil is a more powerful stimulant to the activity of the external secretory function of the pancreas than is edestin or arrowroot starch. These findings show that the liver and pancreatic external functions were apparently stimulated to normal activity regardless of the reaction of the duodenal contents obtained from the proximal portion of the second part of the duodenum (about 5 to 10 cm from the distal end of the pyloric sphincter).

Tables 1 and 2 concern duodenal contents collected (a) while the patient was fasting, (b) after the ingestion of tap water, and (c) from immediately after the ingestion of food up to the appearance of very dark colored bile. It has been shown⁴ that during these periods of collection the activity of the external functions of the liver and pancreas is much less than after the onset of normal digestion. Nevertheless, the p_H of these duodenal contents lies within the same range as those found in duodenal contents collected over the period during which intestinal digestion was in active progress (Table 3), except for the more acid contents derived from Subject B of Table 3 after the ingestion of edestin. Thus, in these experiments, no demonstrable relation existed between the p_H of duodenal contents and the concentrations of bile and pancreatic juice in them.

The contents of the duodenum were acid for ten and twenty-one minutes before hepatic and pancreatic stimulation occurred in Subjects B and C of Table 2 after the ingestion of olive oil, while such stimula-

tion failed to occur in Subject C of Table 1, although the duodenal contents were acid. These findings, together with the absence of relationship between the p_H of duodenal contents and the concentrations of bile and pancreatic juice in them, offer additional support to the conclusion drawn from previous work,⁴ namely, that under normal conditions acidity is probably not essential for the stimulation of the external functions of the liver and pancreas. However, it is always to be borne in mind that duodenal contents collected in the manner described represent a summation of progressive series of secretory activities. In other words, the properties of any sample are the algebraic sums of the several properties possessed by the many fractions which go to compose the sample. Thus, in a collection period of thirty minutes, it would be quite possible for the secretion of the first few minutes to be acid or alkaline in character, while in the latter portion of the collection time a preponderating amount of the opposite type of material could collect, neutralize the first portion and give a final reaction on its side of the neutral point. This fact connotes the necessity of exercising a large measure of caution in drawing final conclusions.

The work of Myers and McClendon⁷ is of interest in relation to the foregoing discussion. These authors determined the p_H of duodenal contents after the ingestion of meals of the character usually eaten by normal persons. They found that the reaction of the duodenum between three and four hours after meals usually fluctuated around the neutral point. It is inferred from their publication that in many patients the alkaline contents were removed from the region of the duodenum lying immediately distal to the pyloric sphincter. Unfortunately, the details of the collection of duodenal specimens of importance in relation to the interpretation of the work presented here are not given. In general, the figures reported in their publication are comparable to those presented here.

CONCLUSIONS

1 The p_H of duodenal contents varied after the ingestion of various food substances. Duodenal contents were acid after the ingestion of protein and mixture of food substances and alkaline after ingestion of fat and carbohydrate food substances.

2 No relation was found between the p_H of duodenal contents and the stimulation of the flow of bile and pancreatic juice.

3 The findings indicate that the various types of pure food substances had about the same stimulating effect on the external functions of the liver and pancreas as regards the production of buffer substances.

483 Beacon Street

Book Reviews

DIATHERMY AND ITS APPLICATION TO PNEUMONIA By HARRY EATON STEWART, M D , Attending Specialist in Physiotherapy, U S Marine Hospital, New York Paul H Hoeber, Inc , Price \$3

The introductory chapter of this book is devoted to a general discussion, including brief reference to the use of diathermy in the U S Marine service during the war, and to some general remarks, especially in regard to pneumonia

The second chapter discusses diathermy technic, including the method of application to various portions of the body, and the diseased condition to which it is applicable The reviewer is rather skeptical of its value in some of the conditions recommended by the author, as "simple myocardial conditions," to "accelerate absorption of clot after hemiplegia" "In those conditions where general cerebral degeneration sets in, due to arteriosclerosis, this current is a rival of galvanism in its effect on improving the nutrition of brain cells"

The third chapter discusses surgical diathermy, chiefly in malignant tumor and tonsils

Chapters four, five and six are devoted to the treatment of pneumonia The author reports marked lessening of the pleuritic pain and consequent slowing of respiration and lessening of cyanosis Thirty-six patients with lobar pneumonia treated with diathermy gave a mortality of 19.4 per cent In twenty-one controls, the mortality was 38.4 per cent Practically all the treated cases terminated by lysis As the average age of the patients was 35 years, a mortality of 19.4 per cent is not especially striking, when we consider that the mortality in the first 5,000 cases of lobar pneumonia in the army during the war was less than 10 per cent It is true the average age of these patients was considerably under 35 years

The book rather suggests lack of a profound knowledge of pathology and internal medicine on the part of the author and contains a large number of loose statements The possibilities of diathermy should not be ignored, and this book will be useful for those who wish to make a study of this subject

NOSOGRAPHY IN MODERN INTERNAL MEDICINE By KNUD FABER, M D , Professor of Internal Medicine, University of Copenhagen, with an Introductory note by Rufus Cole, M D , Director of Hospital, Rockefeller Institute Twenty-one full page portraits Price, \$3.75 New York Paul B Hoeber, 1923

Under an unfamiliar name, we have here a valuable contribution to medical history Too often writers on medical history have felt it necessary to cover the whole subject from the beginning of the world, with endless notes and innumerable biographies This tendency probably has had much to do with the neglect of the study of medical history Knud Faber has traced the growth of nosography, that is the description of disease, in a masterly and attractive manner As he correctly says, the importance of the nosographic method in investigation has been, and still is, very differently rated by different authorities For this reason, he has made a study, the salient points of which follow

On page 5, he takes up the work of the man "who first consciously and clearly gave clinical observation its place of honor as a scientific method"—Thomas Sydenham, and, in the following twelve pages, he gives a clear and adequate account of Sydenham's work, so far as necessary for this study, and at the same time indicating his limitations

In ten pages more, the ground is covered to the consideration of the Paris school at the beginning of the nineteenth century, the work of Morgagni and

Auenbrugger being appropriately mentioned in connection with the period in which their work was really appreciated Boerhaave is properly described as a brilliant teacher rather than an independent clinical investigator, qualities that characterize also his numerous pupils As the author points out, in this period some advances were made in nosology Varicella, influenza, ergotism, lead poisoning, scurvy, sciatica, trigeminus neuralgia, paraplegia in spinal caries and angina pectoris began to claim attention The author's power of condensation is well shown in his account of Sauvages and Linne

From this time, the author does not travel so rapidly An estimate is made of Pinel, Bichat and Corvisart and the epoch-making Laennec, and their most important pupils are briefly placed In a few words, Faber epitomizes the results of this epoch "The violence with which clinical medicine was completely revolutionized will always remain one of the wonders of medical history"

The Irish clinicians, and also Addison and Bright, are properly appreciated The reference to W W Gerhard, the brilliant American pupil of Louis, reminds one that, although Gerhard and his descendants anglicized the name, leaving the "h" silent, many now pronounce it in the teutonic fashion Skoda, Rokitansky and Schoenlein appropriately close this chapter

The next is devoted to "German physiological medicine," although, as the author points out, Magendie had already initiated the physiologic movement Faber shows the weak points in that movement, in general so fruitful, such as the Vircho-Niemeyer tuberculosis teaching As he says, German physiologic medicine was in the main preparatory, leading up to the new clinical era, through methods developed chiefly by physiologists and chemists In speaking of Claude Bernard, he shows how easy it is for physiologists to miss the clinical point of view An account of the great place filled by Rousseau leads to the name of Pasteur, and the bacteriologic clinic gives the name to a chapter in which the most outstanding discoveries and inventions in specific pathology are described A large chapter is properly devoted to functional diagnosis Many will think too much space is given to the views of Ottomar Rosenbach, interesting as they are In this chapter, the wide range of the author's study is shown by his familiarity with the work of American investigators He points out how the modern advance has finally led to the point that the patient himself can be treated, rather than the disease Gastric ulcer is mentioned as an illustration of the errors into which diagnosis may fall As the study of "hyperacidity" advanced, gastric ulcer became more and more rarely diagnosed, especially in German clinics, and ulcer only came back as a clinical diagnosis after surgery had taken over the old anatomicoclinical diagnosis The French internist, Soupault, is given credit for the innovation In this chapter, Faber discusses with great insight the proper point of view of the clinician

The final chapter is devoted to constitutional pathology, a movement that "belongs almost entirely to the twentieth century, and is directly associated with the influence which modern research on heredity has had on pathology" Nowhere is the boundless extent of the basis of nosography better shown than in its turning to the experiments of Mendel and his successors In this chapter, too, is a discussion of causes, conditions and disposition In his final remarks, the author sums up the essence of nosographic study

The little work will be interesting to clinicians familiar with medical history on account of the skill with which the large subject has been brought within reasonable limits It should be carefully read by all medical students in their early years, especially in the long period in which they hear little of clinical medicine, and that very often in an unsympathetic tone

The publisher has done his work fairly well In these pictorial days, a few more portraits could have been added with advantage Errors in the text are few Welcher (p 80) should be Welcker, and typhus (p 118) typhoid

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PARADOXICAL SHORTENING OF THE COAGULATION TIME OF THE BLOOD AFTER INTRAVENOUS ADMINISTRATION OF SODIUM CITRATE *

NATHAN ROSENTHAL, M.D., AND GEORGE BAEHR, M.D.
NEW YORK

Sodium citrate renders blood incoagulable when the two are mixed in proper proportions in the test tube. Because of its well-known anticoagulant action, it was first employed for blood transfusions in this country by Lewisohn¹ and by Weil,² and abroad by Hustin³ and Agote⁴.

In 1915, while working with Lewisohn¹ on some of the preliminary experimental work, one of us (G. B.) observed a remarkable and apparently paradoxical shortening of the coagulation time of the blood in human beings and dogs following transfusion of the citrated blood. The effect was strikingly brought out in one of these experiments. Blood taken from a dog before a citrate transfusion showed a clotting time of five minutes. Three hundred cubic centimeters of blood was then removed and mixed with 5 cc of 10 per cent sodium citrate solution and re-injected into the jugular vein of the same dog. Blood taken at intervals of three minutes showed a gradually diminishing clotting time, until after one half hour the clotting time was found to be reduced to ten seconds. This experiment was later confirmed by Hedon⁵.

Subsequent experiments demonstrated that this action was due to the sodium citrate and not to the transfused blood. Weil² was the first to report this fact. He injected as much as 5 gm intravenously in a human being and found that the coagulation time of the blood was

* From the Pathological and Medical Departments, Mount Sinai Hospital, New York. The work was done during the tenure of a George Blumenthal, Jr., Fellowship in Pathology.

1 Lewisohn, R. Med Rec 87 141, 1915

2 Weil, Richard. Sodium Citrate in the Transfusion of Blood, J A M A 64 425 (Jan 30) 1915

3 Hustin, A. An et bull Soc roy d sc med et nat de Bruxelles 72 104, 1914

4 Agote, L. An d Inst mod de clin med, Buenos Aires 1 25, 1915

5 Hedon, E. Presse méd 26 57 (Feb 4) 1918

reduced by one-half about ten minutes after the injection. These observations have recently been amply confirmed by Neuhof and Hirschfeld⁶ in a large series of surgical cases, using even larger doses than Weil (up to 9 gm). They recommend the employment of sodium citrate in cases of hemorrhage and when a relatively bloodless operation is desired.

During the last four years, we have repeatedly employed this means of arresting secondary hemorrhages in a variety of medical conditions such as gastric ulcer, pulmonary tuberculosis, cerebral hemorrhage, typhoid fever and excessive bleeding from a tooth socket following extraction, and after tonsillectomy. From 3 to 6 cc of a 30 per cent solution of sodium citrate (3 to 6 gm) has usually been administered, very slowly, the intravenous injection taking from ten to fifteen minutes for completion.

We have not been able to convince ourselves that the intramuscular administration recommended by Neuhof and Hirschfeld⁷ is by any means as efficacious. Leone⁸ did not find any diminution of blood coagulation after intravenous injection of sodium citrate. But he used toxic doses. We have limited ourselves to its intravenous use in spite of the fact that its employment is not entirely without danger. In one case,⁶ not in our hands, it has been followed by a fatality, undoubtedly due to a too hasty administration. If properly administered, from 3 to 6 gm can be safely given to an adult of average size. In blood diseases, for reasons subsequently to be developed in this paper, its employment is at all times contraindicated.

This striking phenomenon, shortening the coagulation time of the blood, the exact opposite of what occurs *in vitro*, was made the subject of a detailed experimental study in order to ascertain what changes were induced by sodium citrate in the complicated mechanism of blood coagulation. For this purpose the effect on each factor involved in coagulation was studied individually.

MATERIAL AND TECHNIC

Chemically pure sodium citrate was used for the solutions. Although the effect on dogs is probably more pronounced, cats were selected as the animals of choice in the laboratory, because they were more easily obtainable. Blood was withdrawn from various vessels (carotids, jugulars and femorals), preferably with an all-glass syringe or a cannula, before and after the intravenous injection of sodium citrate. The syringes were sterilized and washed with saline solution before use. Usually, 15 cc of blood was removed for each observation and divided

6 Neuhoef, H., and Hirschfeld, S. New York M J 95:113, 1915.

7 Neuhoef, H., and Hirschfeld, S. Ann Surg 76:1 (July) 1922.

8 Leone, G. Riforma med 38:313 (April 3) 1922.

in two small test tubes. For the purpose of determining the coagulation time, half of the sample was put into a small test tube previously washed with saline solution (Lee and White⁹), and the rest of the blood was put into a second small test tube containing 0.03 cc. of a 30 per cent solution of sodium citrate. The second tube was immediately shaken in order to mix the blood and sodium citrate, and it was then allowed to stand about one half hour or longer to insure the sedimentation of the red blood cells so that the blood platelets could be easily counted in the supernatant plasma.

The citrate solution was injected very slowly because otherwise death from cardiac or respiratory failure rapidly ensued.¹⁰ In a favorable experiment, the shortening of coagulation time begins within ten minutes and reaches its maximum within one hour.

Calcium—Sodium citrate exerts its anticoagulant effect *in vitro* by a change in the calcium balance of the blood as shown by Sabbatani.¹¹ It might therefore be anticipated that the opposite effect which it exerts *in vivo* is also caused by a variation in the blood calcium. However, two sets of observations immediately contradict this possibility. First, we have been unable to find any change in the calcium content of the blood after intravenous administration of sodium citrate. The analyses were performed by Dr J. S. Kohn, and are in agreement with the old observations of Sabbatani.¹² Secondly, the calcium in normal blood appears to be the optimum amount needed for coagulation (Clowes¹³). The addition of variable quantities of calcium chloride to normal blood influences the rate of coagulation either very little or not at all.

Sodium citrate forms a loose compound with the inorganic calcium and does not remain in the blood stream long enough to be a factor (Salant)¹⁴. Vines¹⁵ has shown that it is the organic combined calcium that is of importance in blood coagulation. We could therefore eliminate calcium as the responsible factor in the hastening of blood coagulation after the intravenous injection of sodium citrate.

Fibrinogen—The fibrinogen content of human and of cat's blood before and after citrate administration was determined according to

9 Lee, R. I., and White, P. D. Am J M Sc 145:495, 1913.

10 When sufficient sodium citrate was injected to induce death of the animal, the blood within the heart and great vessels was found to be incoagulable. When it recalcified this blood it coagulated promptly, an indication that death was due to calcium deprivation and not to any anaphylaxis-like phenomenon. When a large toxic dose was injected, the blood also became incoagulable but clotted on recalcification. The effect was due to the sodium citrate present in the blood stream, producing the same effect as in the test tube. This has also been noted by L. Sabbatani (Atti d r Accad d sc di Torino 36:1, 27, 1901).

11 Sabbatani, L. Compt. rend. Soc de Biol 54:716, 1902.

12 Clowes, G. H. J. Physical Chem 20:407, 1916.

13 Salant, W., and Wise, L. E. Jour. Biol. Chem. 28:27 (Dec.) 1916.

14 Vines, H. W. C. J. Physiol. 55:85 (Mar.), 1921.

Gram's¹⁵ method and also the most recently suggested method of Foster and Whipple¹⁶. No appreciable difference in the content of fibrinogen was observed after the injection, even when the coagulating time of the blood had been shortened to less than half. An increase in the amount of fibrinogen was thereby eliminated as the responsible factor.

Antithrombin—The so-called antithrombin factor described by Howell as often responsible for variations in the relative coagulability of blood was also eliminated from consideration. We carried out observations in accordance with Howell's¹⁷ and Hess's¹⁸ recommendations and could find no change in this theoretical factor after the citrate had been injected.

Cytozyme and Serozyme (Thiomboplastic Substance and Prothrombin)—Howell's¹⁷ method of demonstrating the relative amount of prothrombin (or serozyme) was also employed. This theoretical precursor of thrombin (according to Howell) is studied by collecting the blood in sufficient potassium oxalate to prevent coagulation. The so-called prothrombin time is the coagulating time of the oxalated plasma after recalcification. We found that after injection of the sodium citrate, the prothrombin time was shortened, often in exact proportion to the diminution in the coagulation time of the whole blood.

Unfortunately, the results were not altogether constant. On investigation, this inconstancy was found to depend on the length of time that intervened between the drawing of the blood into the oxalate and its subsequent recalcification. If the oxalated blood was recalcified immediately after being drawn, the so-called prothrombin time was equivalent to the coagulation time of the unoxalated blood. If the oxalated blood was allowed to stand for ten or fifteen minutes before being recalcified, the prothrombin time was greatly reduced, perhaps from five minutes to one minute. We have therefore been unable to convince ourselves of the absolute accuracy of any of the quantitative observations on prothrombin. Citrated blood acts in similar and even more marked fashion than oxalated blood, so that the citrate method recommended by Gram¹⁹ for blood coagulation cannot be considered reliable. However, when the specimens of oxalated or citrated blood drawn before and after the injection of sodium citrate were all recalcified at the same intervals after being drawn, the prothrombin time was found to be definitely shortened at the time after injection when the clotting time of the whole blood is

15 Gram, H C Jour Biol Chem **49** 279 (Dec) 1921

16 Foster, D P, and Whipple, G H Am J Physiol **58** 365 (Jan) 1922

17 Howell, W H Condition of the Blood in Hemophilia, Thrombosis and Purpura, Arch Int Med **13** 76 (Jan) 1914

18 Hess, A F J Exper Med **21** 338, 1915

19 Gram, H C Bull Johns Hopkins Hosp **31** 364 (Oct) 1920

shortened. One can say, therefore, that during the period after injection when the clotting time is shortened, there is a marked increase in the activity of some thromboplastic substance in the plasma.

Blood Platelets.—In view of the fact that the chief source of the activating agent for blood coagulation is believed to be the blood platelets, careful counts of the platelets (in the plasma) were made before and at intervals after the administration of the sodium citrate.

The experiments were first checked up by a control experiment in which the procedure was the same except that the sodium citrate injection was omitted (Table 1).

It will be noted in Table 1 that the clotting times and blood platelet counts show only slight variations.

TABLE 1.—*Control Experiment*

Time	Coagulation Time	Blood Platelets
3 15	5 min	352,000
3 25	6 min	322,000
3 29	7 min	313,000
3 34	7 min	316,000
3 46	6 min	352,000
3 55	6 min	313,000
4 00	7 min	345,800

TABLE 2.—*Effect of intravenous injection of 0.3 to 0.5 Gm Sodium Citrate*

	Cat 3		Cat 4		Cat 11		Cat 12		Cat 13	
	Coagu lition Time, Min	Blood* Plate- lets								
Before injection										
5 minutes later	8	620,800	11	139,200	11	569,600	14	640,000	8	429,000
10 minutes later	4	60,800†	3	1,560,000	9	448,000	12	521,000	8	256,000
20 minutes later	1½	270,000	2½	739,600	6	512,000	3	96,000‡	1½	384,000
40 minutes later	1½	510,000	2½	646,000	4	384,000	2	478,000	2½	320,000
50 minutes later					1½	368,000	3	325,000	2	325,000
									1½	287,000

* In plasma

† No clot retraction

‡ Slight clot retraction

When sodium citrate is injected intravenously, the blood platelets frequently show an immediate diminution, but then number more or less quickly returns to normal.

The experiments outlined in Table 2 illustrate this point.

An analysis of the experiments in Table 2 reveals that the intravenous injection of 0.5 gm of sodium citrate in the cat results in the following changes:

1 A marked reduction in the coagulation time which begins within five minutes after the injection and reaches its maximum from one half

to one hour later. The maximum effect in Cat 11 represented a reduction in coagulation time from eleven minutes to one and one-half minutes.

2 A marked reduction in the number of blood platelets in the circulating blood. The most pronounced reduction was observed in Cat 3, in which the count was reduced from 620,800 to 60,800 within ten minutes after the injection. In some instances, the reduction is less marked and occurs more slowly. Within one-half hour, however, the count begins to rise toward normal.

3 When the blood platelet count reaches a very low point (as occurred ten minutes after injection in Cat 3 and fifteen minutes after in Cat 12), the clot resulting from the coagulation fails to retract. This confirms the accuracy of the low platelet counts.

4 The blood platelet counts would seem to indicate that between ten and fifteen minutes after the injection in Cats 3 and 12, more than 85 and 90 per cent of the platelets had been suddenly destroyed or removed from the systemic circulation.

5 Although both a reduction in blood platelets and in the coagulating time of the blood is appreciable five minutes after the injection, the period of maximum reduction in platelets by no means corresponds to the period of maximum shortening in the coagulation time. In fact, the two curves never run parallel. The reduction in blood platelets reaches its maximum very rapidly and returns toward normal within a half hour as a rule, whereas the maximum shortening in the coagulating time of the blood occurs from one half to one hour after the injection (when the platelet count is often already back to normal), and may persist at this level for several hours and then only slowly return to normal within the succeeding twenty-four hours.

The impression gained, therefore, from these experiments is that the primary process is a destruction or removal of blood platelets from the circulating blood. If the platelets were reduced by a mere destruction within the circulating blood, the maximum shortening in the coagulating time would have occurred simultaneously with the maximum reduction in blood platelets. The platelets that had been in contact with the sodium citrate must therefore have been removed from the blood by some organ, perhaps the spleen or by the blood phagocytes and then gradually destroyed, thromboplastic substance (cytozyme) being thereby gradually liberated into the circulation. The spleen seems to us the more likely agent for the removal and destruction of platelets in view of the unquestioned rôle it plays in the similar mechanism involved in the so-called thrombocytopenic purpura (Kaznelson,²⁰ Brill and

20 Kaznelson, P. Ztschr f klin Med 87:133, 1919.

Rosenthal²¹) Furthermore, it is inconceivable that the blood phagocytes would be capable of removing a large number of the platelets from the circulating blood within a few minutes

If our interpretation of the above described phenomena is true, the entire process already has its analogy in toluylendiamin poisoning. The difference between the action on blood of toluylendiamin and of sodium citrate is chiefly a difference in point of attack, the former affecting red blood cells, the latter the blood platelets. Toluylendiamin according to Joannovics and Pick²² does not destroy red blood cells *in vitro*, but it does something to them because red cells which have been in contact with the chemical are rapidly removed from the circulation by the spleen and there destroyed. Similarly, sodium citrate does not destroy platelets *in vitro*; it preserves them in the test tube. In fact, this preservative action is employed as the basis for the use of sodium citrate in the present methods of counting blood platelets. After being in contact with sodium citrate, the platelets are suddenly and rapidly removed from the circulation, probably by the spleen, and then destroyed. The destruction of red cells after toluylendiamin poisoning is followed by the flooding of the body with the contents of the red cells, the blood pigments, with the resultant development of jaundice. The destruction of the blood platelets is followed by a discharge into the blood of their contents, the thromboplastic substance cytozyme, with the resultant shortening of the coagulation time of the blood.

This gradual destruction of blood platelets after their removal from the blood will account for the fact that the amount of cytozyme in the blood (as indicated by the coagulability) is often still increasing long after the blood platelet count has returned to within normal limits.

Mobilization of Blood Platelets—The ease and rapidity with which the body can restore the total number of blood platelets after a large number have been removed from the circulation is, we believe, an important observation. The body is apparently able to mobilize large numbers of fresh platelets within a few minutes. In a few instances in humans and cats in which we have seen only relatively slight changes in the platelet count, this mobilization of fresh platelets may have occurred simultaneously with the withdrawal of the damaged platelets from the circulation, and so have partly masked any reduction in the number.

Such a mobile mechanism is needed as one of our most important defensive measures, for the arresting of hemorrhage and the primary formation of thrombi in the living body are produced by the agglutina-

21 Brill, N. E., and Rosenthal, N. Am J M Sc 166 503 (Oct) 1923

22 Joannovics, G., and Pick, E. P. Ztschr f Exper Path u Therap 7 185, 1909

tion of blood platelets. The better known coagulation phenomena usually play only a secondary rôle, at least so long as the circulation is uninterrupted.

FURTHER TESTS OF THE THEORY

The above described theory, although it accounts for all the phenomena observed after the intravenous injection of sodium citrate and satisfactorily explains the shortening in the coagulation time, was subjected to two other series of experiments. If our explanation was correct, we felt that it would be important to study the effect of sodium citrate on animals that normally do not possess any blood platelets comparable to the mammalian, and also on human beings in whom, because of disease, there existed a marked numerical deficiency or disease of the platelets.

TABLE 3—*Coagulation Time of Blood After Intravenous Injection of Sodium Citrate*

	Duck 1	Duck 2
Before citrate administration	5 min	1 hour
Amount injected	0.5 gm	0.25 gm
5 minutes later	25 min	1 hour
7½ minutes later	20 min	
20 minutes later	24 min	1 hour, 20 min
40 minutes later	14 min	
48 minutes later	0.25 gm sod citrate intraven	
54 minutes later	11 min	
1 hour, 5 minutes later	27 min	
1 hour, 20 minutes later	16 min	

Observations on Ducks.—Ducks are known to have no blood platelets. At least, the thrombocytes or homologues of the mammalian platelets are few in number.

Two ducks were used for the investigation. The wing vessels served well for the removal of the blood and for the injection of the citrate. One duck was injected with 0.25 gm, the other with 0.5 gm.

As can be judged from Table 3, the intravenous injection of sodium citrate in ducks either exhibits no effect on the coagulating time, or else produces a distinct prolongation. No period of shortening of coagulation time is demonstrable—a distinct contrast to the effect observed in animals that possess well developed platelets (cat, dog and human being).

Deleterious Effect of Sodium Citrate in Hemorrhagic Diseases.—The various hemorrhagic diseases are for the most part characterized by either a marked numerical or a qualitative deficiency in the blood platelets. It was therefore thought to be important to ascertain the effect of sodium citrate in these conditions. It was administered intravenously in two cases, each representing a separate clinical type of primary hemorrhagic blood disease, (1) essential thrombopenic purpura (the

so-called purpura hemorrhagica), which is characterized by a pronounced diminution in the number of blood platelets; (2) congenital hemophilia, in which the number of blood platelets is normal but in which the coagulation time of the blood is prolonged possibly because of some qualitative deficiency in the platelets

REPORT OF CASES

CASE 1—Essential Thrombopenia (Purpura Hemorrhagica) This patient had a generalized purpuric skin eruption and was bleeding from the gums and nose. The blood examination revealed hemoglobin, 90 per cent., red cells, 4,864,000, white cells, 8,200, blood platelets, 300 (counted in undiluted plasma), differential count polymorphonuclear neutrophils, 54.0 per cent, eosinophils, 3.0 per cent, basophils, 0.5 per cent, myelocytes, neutrophilic, 0.5 per cent lymphocytes, 31.5 per cent, monocytes, 4.5 per cent. The coagulation time was eight minutes, bleeding time (ear), twenty-five minutes. In the capillary resistance test (Hess²³) numerous petechiae appeared within five minutes. There was no retraction of the blood clot for eight hours.

The remarkably low blood platelet count, the normal coagulation time contrasted with the prolonged bleeding time, the positive capillary resistance test and nonretraction of the blood clot showed that the case was a true purpura (essential thrombocytopenia).

TABLE 4—Findings in Case 2

	Coagulation Time	Blood Platelets
Before sodium citrate injection	45 min	192,000
15 minutes after	15 min	250,000
2 hours 20 minutes after	46 min	170,000
3½ hours after	25 min	120,000
24 hours after	1 hr, 25 min	140,000
48 hours after	3 hrs (soft clot)	110,000
72 hours after	25 min	260,000

Six days after admission, the patient received a slow intravenous injection of 4.5 gm of sodium citrate. The bleeding from the gums became worse the next day. The coagulation time of the blood increased gradually after the injection. The clotting time of the blood immediately before the injection of citrate was four minutes.

The citrate was injected slowly for twelve minutes when it was stopped on account of the patient's complaining. Two minutes after sodium citrate injection the coagulation time was four minutes, eighteen minutes after, ten minutes one hour and thirty minutes after, sixteen minutes, eighteen hours after seventeen minutes.

The prolongation of the clotting time is interesting in view of the similar effect described above in animals which have few or no blood platelets. Blood platelet counts were also made at the same time that the tests for blood coagulation were performed. The platelets were counted in the undiluted citrated plasma.

Before the citrate injection the platelets numbered 400 per cubic millimeter, two minutes after injection they numbered 400, eighteen minutes after 300, one hour and thirty minutes after 200, eighteen hours after 150. The reduction in the number of blood platelets following the injection of sodium citrate runs parallel with the increased coagulation time.

CASE 2—Congenital Hemophilia One observation on this disease has already been published by Ottenberg.²⁴ In 1916, he injected 0.6 gm of sodium citrate

23 Hess A F Hemophilia, Arch Int Med 17:203 (Feb) 1916

24 Ottenberg, R Proc Soc Exper Biol & Med 13:1011, 1916

intravenously in a patient suffering from congenital hemophilia and observed that the coagulation time of the blood was shortened from ninety-five to twenty-five minutes. Forty-eight hours later, the coagulation time was prolonged to two hours and twenty-five minutes.

Our own observations confirm this finding. We injected 30 gm of sodium citrate in a hemophilic patient who has been repeatedly admitted to the hospital for bleeding from the gums or hemarthroses. The result is summarized in Table 4.

Sodium citrate produces in hemophiliacs early shortening in coagulation time exactly as it does in normal individuals, but this shortening is purely transitory and is followed twenty-four and forty-eight hours later by a pronounced prolongation in coagulation time and by an increase in the bleeding tendency. The explanation for this deviation from the normal result is not obvious. It is possibly dependent on an accentuation of the qualitative deficiency in the blood platelets. In addition, the prolongation of coagulation time twenty-four and forty-eight hours after the injection was associated with a pronounced reduction in the number of blood platelets.

Our experience with sodium citrate in the hemorrhagic diseases is sufficient to indicate that it is not only an ineffective remedy, but actually a dangerous one in these conditions. Instead of producing a shortening of the coagulation time of the blood as in normal individuals, it produces a pronounced delay in coagulation. In those conditions characterized by a marked numerical deficiency in blood platelets (*purpura hemorrhagica*), it may result in almost complete disappearance of platelets from the circulating blood and a definite increase in the bleeding tendency.

SUMMARY

Sodium citrate, when administered intravenously in large doses (0.5 gm for dog or cat, from 30 to 80 gm for man), produces a pronounced and progressive shortening in coagulation time of the blood, which usually reaches its maximum within one hour and may persist for many hours. As a rule, the coagulation time slowly returns to normal within twenty-four hours.

This action of sodium citrate on the coagulation of the blood *in vivo* is exactly opposite to that occurring *in vitro*. We believe that it is dependent on some effect on the blood platelets, which are not directly destroyed by the citrate but are damaged by contact with it and are then removed from the circulation by the spleen or other organs, where they are destroyed and their thromboplastic contents gradually liberated into the circulating blood. This theory is based on the following observations:

1 In the test tube, sodium citrate does not destroy the platelets, but it affects them so that they are actually preserved and are therefore more easily counted.

2 Within a few minutes after the intravenous injection of sodium citrate, the blood platelets often begin to diminish in number, the maximum reduction being usually observed after from ten to fifteen minutes and the number as a rule returning to normal after from one half to one hour. The greatest reduction in blood platelets was observed in cats, in two of which 85 and 90 per cent of the platelets disappeared from the circulating blood within ten and fifteen minutes, respectively, and the count again reached normal a half hour after the injection.

3 Increasing amounts of free thromboplastic substance (cytozyme) probably derived from platelets, begin to appear in the blood stream as the coagulation time is shortened.

4 No changes in the content of the blood as to the other factors concerned in coagulation, such as calcium, fibrinogen or antithrombin, are demonstrable.

5 The increase in the thromboplastic agent cytozyme and the shortening in coagulation time of the blood do not occur simultaneously with the numerical change in the platelets, but follow it. The maximum shortening in coagulation time occurs some time after the numbers of platelets have again returned to normal, and persists for hours.

6 The characteristic shortening of coagulation time after intravenous injection of sodium citrate does not occur in animals (ducks) in whose blood few or no platelets occur. If sufficient citrate is administered, the opposite effect is produced in such animals and the coagulation time may be markedly prolonged.

7 The shortening of coagulation time after intravenous injection of sodium citrate likewise fails to occur in human beings suffering from hemorrhagic blood diseases that are characterized by a pronounced numerical deficiency in blood platelets. In purpura hemorrhagica, in which such a reduction in the number of platelets is regularly present, the injection of sodium citrate may be followed by almost complete disappearance of platelets from the circulating blood and a prolongation of the clotting time.

In congenital hemophilia, in which there is presumed to be some deficiency in the quality of blood platelets, the injection of sodium citrate is followed by a prolongation in the coagulation time, a diminution of the blood platelets and a marked increase in the bleeding tendency.

Sufficient evidence has been presented, therefore, to indicate that the shortening of coagulation time after injection of sodium citrate in normal individuals or animals is due to some influence on the blood platelets.

That this is not a direct destruction is proved by the test tube experiment and by the fact that the maximum shortening of coagulation times does not occur simultaneously with the maximum reduction in platelets, but follows from ten minutes to one hour later. This sequence suggests that the platelets after contact with the citrate are damaged and removed from the circulation by some organ, there destroyed, and their thromboplastic contents gradually liberated into the blood stream. The removal or modification of damaged or altered blood platelets is probably one of the functions of the spleen, especially in view of the rôle that it is presumed to play in chronic thrombocytopenia or purpura hemorrhagica.

With these observations as a basis, the slow intravenous injection of large doses of sodium citrate up to 5 gm has been successfully employed in arresting hemorrhages due to gastric ulcer, typhoid fever, pulmonary tuberculosis and other bleeding conditions that are not accompanied by diminution or disease of the blood platelets.

Although the coagulation time of the blood is often materially shortened, no tendency to intravascular thrombosis has ever been observed, and we believe that this possibility can be dismissed as an unlikely danger. The real danger to be guarded against is a too hasty injection. The citrate should be well diluted and the procedure should take at least fifteen minutes continuously, not intermittently, during that period, to avoid too great a concentration in the heart's blood at any one time. For the sake of absolute safety, and because of other manifest advantages, we would advise its administration in from 200 to 500 c.c. of blood in the form of the citrate transfusion of Lewisohn.

In hemorrhagic blood diseases, for reasons detailed above, its use is strictly contraindicated.

NARCOTIC DRUG ADDICTION

II THE PRESENCE OF TOXIC SUBSTANCES IN THE BLOOD SERUM IN MORPHIN HABITUATION *

EMIL J PELLINI MD
AND
ARTHUR D GREENFIELD, AB
NEW YORK

In our first paper in this series on narcotic drug addiction¹ we dealt with the question whether the continuous taking of morphin causes the presence in the blood serum of any substance which has a protective effect against morphin, and arrived at negative conclusions

Another question is whether any specific toxic substance is produced by morphin habituation. This question, which is closely related to the first, has a more direct practical bearing on the current theories of the nature of morphin addiction and the causation of withdrawal symptoms and also on treatment. There has been considerable controversy on this subject and a more or less widespread belief that there is such a substance and that it is the cause of the well known symptoms of morphin withdrawal when no longer neutralized by the continued administration of morphin and some methods of treatment of drug addiction have been founded upon this belief

The scientific basis for this conception originally rested upon the work of Marme² who reported the finding of oxydimorphin in the feces, lungs and liver of dogs habituated to morphin. He further stated that oxydimorphin produced symptoms similar to those of morphin withdrawal when injected into nontolerant dogs. Marme's results have been disproved by numerous subsequent investigators³

The belief is at present based solely upon the work of Valenti⁴ who, in 1914 reported a series of experiments in which he investigated the effects produced on the circulation of normal dogs by the intravenous injection of serum of the blood of dogs accustomed to increasing doses of morphin and which were in withdrawal when the blood was

* From the Department of Pharmacology, University and Bellevue Hospital Medical College

1 Pellini, E J and Greenfield, A D Arch Int Med 23 279 (Sept) 1920

2 Marmé Deutsch med Wchnschr 14 197, 1883

3 A review of this work is contained in an article by Du Mez, A G Increased Tolerance and Withdrawal Phenomena in Chronic Morphinism, J A M A 72 1069 (April 12) 1919

4 Valenti Arch f exper Path u Pharmakol 75 437, 1914

obtained. Since his results have never been tested by other investigators, we have made the study of this question the subject of the present paper.

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XXII ADRIANO VALENTI

Versuch 6

Hund von 9 kg, Tracheotomie, linke Carotis, rechte Jugularis externa. Das diesem Tier injizierte Serum stammte von einem Hund von 11 kg, dieser war 55 Tage lang mit Morphin behandelt worden, beginnend mit 0,1 g und langsam ansteigend bis zu einer Tagesmenge von 3,15 g Morphin hydrochloricum subkutan, wobei es im ganzen 69,95 g erhielt. Der Aderlaß an der Vena femoralis wurde am dritten Tage der Abstinenz ausgeführt, und 190 ccm Blut aufgefangen, das zentrifugiert 80 ccm zitronengelbes Serum ergibt.

Zeit Uhr	Höchste und niedrigste Puls- frequenz in einer halben Minute	Höchster und niedrigster Blut- druck in Millimeter Quecksilber	Bemerkungen
9,34	66	160—164	Normal
9,44	60	158—162	,
9,51	60	154—162	,
9,58	—	—	Es wird mit der Seruminjektion begonnen
10,3	54—60	170—178	Nach 5 ccm
10,6	66—72	154—162	, 8 ,
10,9	72—78	152—162	, 11 ,
10,15	72—108	150—164	, 17 ,
10,18	72—108	140—164	, 20 ,
10,20	66—90	150—164	, 22
10,24	72—108	140—160	, 26 ,
10,25	66—68	164—174	, 27 ,
10,26	—	—	Die Injektion wird unterbrochen
10,30	78—78	154—162	
10,33	72—90	144—162	
10,34	—	—	Die Injektion wird fortgesetzt
10,40	72—78	150—162	Nach 33 ccm
10,43	72—84	142—160	, 36 ,
10,48	66—96	132—154	, 40 ,
10,51	60—72	140—154	Die Injektion wird sistiert
10,55	78—90	140—152	
10,59	66—72	140—152	
11,10	74	152—156	

Fig 1.—Reproduction of a page of Valenti's article containing a protocol of an experiment giving figures of normal pulse rate and blood pressure and variations following the injection of serum from a dog in the withdrawal stage.

Valenti's first work consisted in injecting into normal dogs the blood serum from dogs which he had addicted to morphin, and from which the morphin had been withdrawn for a period of three days at the time

of obtaining the blood. A typical experiment is most easily shown by reproducing one of his protocols (Figs 1 and 2). He found certain circulatory disturbances, namely arrhythmia and marked increase in

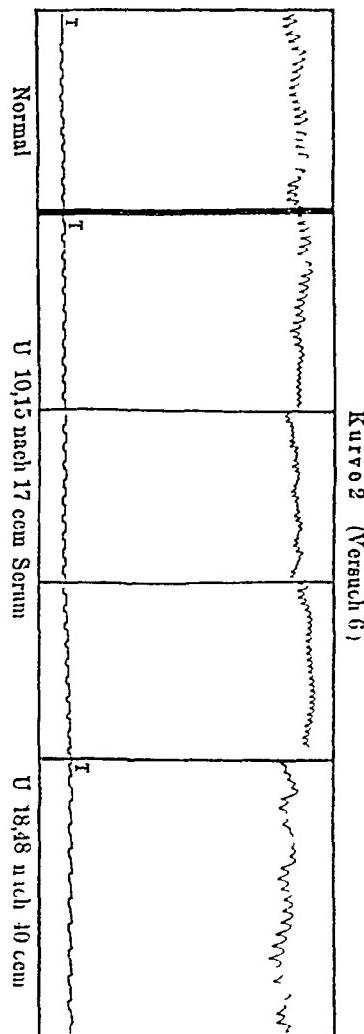
Experimentelle Untersuchungen üb d chronischen Morphinismus usw 447

Tabelle 6

Blutdruck in Millimeter Quecksilber	höchster niedrigster	Vor	Nach
		der Injektion	
164	10 mm	178	
154		152	26 mm
No 6		No 48	

Pulsfrequenz in einer halben Minute	höchste niedrigste	Vor	Nach
66	60	108	
60		60	
No 6		No 48	

Es zeigt sich also sehr deutlich, daß, obgleich geringere Serum Mengen als bei den anderen Tieren injiziert wurden, diese imstande sind, größere Schwankungen des Blutdruckes und des Pulses hervorzurufen, vor allem aber erscheint bei diesem Versuch das Phänomen der Schwankungen im Herzrhythmus im gleichen Zeitabschnitt sehr auffällig. In der zweiten hier angeschlossenen Kurve sind wenigstens drei verschiedene Pulsrhythmen zu bemerken, und diese Arrhythmien hielten den ganzen Versuch hindurch an, was aus den kurzen hier angeführten Kurven besser als aus den Zahlen zu ersehen ist.



Versuch 7

Hündin von 6,4 kg, Tiacheotomie, linke Carotis, rechte Jugularis externa. Das diesem Tier injizierte Serum stammt aus dem Blut eines Hundes von 9,6 kg, der in 48 Tagen bei einer Anfangsdagesdosis von 0,02 bis zu

Fig 2—Continuation of Figure 1 giving a table showing maximum variations in pulse rate and blood pressure before and after serum injection and a tracing of carotid blood pressure from which these figures are obtained.

variability of the heart rate and blood pressure. Control experiments, using serum from the blood of normal dogs, showed but slight deviations.

He next undertook to determine whether there is any relation between the total amount of morphin administered to the addicted dogs and the degree of circulatory disturbances produced by their serum. He concludes that more pronounced effects are produced by the serum of the dogs receiving the largest total amount of morphin during the period of addiction.

He then investigated the question whether the intensity of the effects produced by the serum was in direct relation to the length of the period of withdrawal. He injected serum of blood drawn from dogs from which the morphin had been withdrawn for periods of thirty-six hours, ten days and twenty days, respectively. Under similar conditions as to total amount of morphin administered, the period of withdrawal appeared to have no relation to the intensity of the circulatory effects produced by the serum.

His concluding experiments were to determine whether circulatory disturbances similar to those produced by injecting the serum of addicted dogs into normal dogs could be found in the addicted dogs themselves during the period of withdrawal. He took the blood pressure and heart rate of dogs before addiction and at thirty-six hours, three days and twenty-one days, respectively, after withdrawal. He reports the same type of circulatory disturbances in these animals as in the normal dogs injected with serum of addicted dogs. During observation of the blood pressure and heart rate, he administered by subcutaneous injection increasing doses of morphin solution until the dose which the animals had received on the last day of their morphinization period had been passed. The disturbances became gradually weaker, and finally disappeared as soon as the previously accustomed dose was reached. A dose slightly over this produced the definite "morphin pulse," as in a dog not accustomed to morphin.

EXPERIMENTAL WORK

Our work consisted of duplication of the most significant feature of Valenti's work and of additional tests of our own. The latter comprised electrocardiographic studies, injection of serum into cats with a view to observing any effects on behavior or general symptoms, and studies of the chemistry of the blood of habituated dogs.

In duplicating Valenti's work, the first question that suggested itself was the form of anesthesia to be used. Valenti fails to state what anesthetic he used, in fact, he does not specifically state that he used any. As he subjected the normal dogs into which the serum was injected to tracheotomy, and specifies only in the cases of the morphinized dogs, on which he made direct observations, that the experiments were performed without tracheotomy and without narcosis, it

is fair to assume that in all the serum injection experiments he used ether by inhalation. We therefore made preliminary tests with ether administered in the customary way. With this method, we were unable to maintain a sufficiently uniform light anesthesia even when the ether was given through a cannula in the trachea, to prevent the occurrence of circulatory variations due to variability in the degree of anesthesia.

We then attempted to use fixed anesthetics such as chlorethane, but found that the dose required to maintain continued, uniform anesthesia produced too great circulatory depression, making the circulation not sufficiently sensitive to possible slight effects of the fluid injected. We were thus brought to the necessity of adopting some method by which anesthesia could be maintained indefinitely at a uniform degree while the circulation was allowed to retain its normal lability.

At this stage of our work we came in contact with Dr Ben Morgan, who had recently perfected a new apparatus for the uniform administration of ether, embodying the principles of rebreathing and positive pressure, and permitting exact control of the amount of ether administered.⁵ We were fortunate in obtaining the personal assistance of Dr Morgan in administering ether for us by his method.

Our method of obtaining the serum for injection was as follows. A male dog of 17.5 kg was habituated to morphin throughout a period of ten months. At the start, 10 mg of morphin hydrochlorid per day was administered subcutaneously, and the dose was gradually increased to 275 gm a day, which was given daily during the last month of the period. During the ten months, the animal lost 3 kg, but showed no other evidences of malnutrition. The total amount of morphin hydrochlorid administered throughout the period was 168.62 gm.

The question had arisen in our minds as to the point of time, after stoppage of morphin administration, at which the blood should be withdrawn to obtain the serum for injection. We noted that Valenti experimented with serum of blood obtained at various stages of withdrawal, and reports that no difference in effects is observed when the blood is drawn at any time from thirty-six hours to twenty days. It occurred to us that if there is any toxic substance in the blood of a morphin habituated dog, such substance should be present in maximum amount or strength at the time of greatest intensity of the withdrawal symptoms. It therefore seemed advisable to ascertain this time before proceeding further. As we had been unable to observe any gross symptoms at any time after the withdrawal of the morphin which would indicate a stage of maximum intensity, and since our work was directed especially toward circulatory changes, we made electrocardiographic

5 Morgan, Ben. Modern Hosp 5 215, 1915.

studies of the heart rate of habituated dogs at various stages of withdrawal. This work was done on other dogs which we had habituated to morphin and showed that the heart rate rises after withdrawal to a maximum point, which is reached in about forty hours, and followed by a gradual decline, reaching normal during a period of from two to three weeks.

We drew the blood for this experiment forty-one and one-half hours after the dog had received the last dose of morphin. Electrocardiographic observations were made on this dog, the second one being made just before obtaining the blood. Table 1 shows the results.

Our technic was as follows. The blood was collected by means of a large gage hypodermic needle thrust through the skin and into the external jugular vein. It was allowed to flow into 50 c.c. centrifuge tubes and was immediately centrifuged and decanted. By this procedure, any possible effect of a local anesthetic was obviated. In order to avoid possible deterioration of the serum, it was used the same day.

TABLE 1.—Effect of Morphin Withdrawal on Heart Rate

Time After Withdrawal	Heart Rate per Min
18 hours	131
41 hours	146
70½ hours	119
94 hours	119
115 hours	124
2 weeks	99
3 weeks	108

The normal dog used for the purpose of testing the effects of the above mentioned serum was a male dog weighing 10 kg. The ether was administered first through a mask, and when surgical anesthesia was obtained the left carotid artery, the left external jugular vein and the trachea were exposed, and a cannula inserted in each. The animal was then placed on its side, the tracheal cannula was connected to the ether apparatus, the artery to a mercury manometer and the vein to the buret containing the serum. The dog was kept warm by coverings and by an electric hot plate placed under the dog board. The buret containing the serum was water-jacketed and the serum maintained uniformly at body temperature.

On completion of the operative procedures, the administration of ether was regulated until the optimum depth of anesthesia was reached, as ascertained by the corneal reflex. This occurred about five minutes before the first normal record was taken, and the rate of ether administration remained constant from that time until the close of the experiment. Observations of the corneal reflex at frequent intervals during the progress of the experiment showed that the optimum depth of

anesthesia was preserved by this rate of administration Table 2 shows the results obtained

In some of his protocols, Valenti gives two readings, both of heart rate and blood pressure, for each point of time Our own records were so lacking in sudden variations that there was no occasion for us to follow his method in this particular

TABLE 2—*Effect of Serum of Morphinized Dog in Withdrawal*

	Time	Heart Rate per Min	Blood Pressure in Mm Hg	Remarks
(a)	2 05	180	170	Before injection
	2 10	195	171	Before injection
	2 15	192	168	Before injection
(b)	2 20	135	166	Before injection Injection of serum started (rate 1 c c per min)
(c)	2 25	186	163	After 5 c c of serum
	2 29	186	158	After 9 c c of serum
	2 32	187	164	After 12 c c of serum
	2 35	187	168	After 15 c c of serum
	2 38	192	166	After 18 c c of serum
	2 41	192	164	After 21 c c of serum
(d)	2 44	195	162	After 24 c c of serum
	2 47	193	158	After 27 c c of serum
	2 50	195	158	After 30 c c of serum
	2 53	195	166	After 33 c c of serum
	2 56	190	164	After 36 c c of serum
	2 59	190	164	After 39 c c of serum
(e)	3 02	190	168	After 42 c c of serum
	3 05	186	164	After 45 c c of serum
	3 08	192	172	After 48 c c of serum
	3 11	195	170	After 51 c c of serum
	3 14	195	162	After 54 c c of serum
	3 17	195	164	After 57 c c of serum
(f)	3 20	195	166	After 60 c c of serum
	3 23	195	164	After 63 c c of serum
	3 26	187	162	After 66 c c of serum Injection stopped
	3 29	195	162	
(g)	3 32	195	158	
	3 35	195	159	
	3 38	195	160	
(h)	3 42	195	162	
	3 45	195	162	
Blood Pressure in Mm Hg			Before Injection	After Injection
Highest			171	172
Lowest			166	158
			—	—
Heart Rate per Min			5	14
Highest			195	198
Lowest			180	186
			—	—
			15	12

We next took, for purposes of comparison, a similar record of a dog injected with normal dog serum, all other conditions being identical The weight of the dog was 9 kg Table 3 gives the results obtained

Figure 4 consists of sections of the record chosen at points corresponding as nearly as possible to those given from the record of the preceding experiment

Comparison of the records obtained with normal serum and serum of the morphinized dog in withdrawal shows no such effects of the latter as were described by Valenti, but in view of the disparity between our results and his, we felt that additional work along somewhat dif-

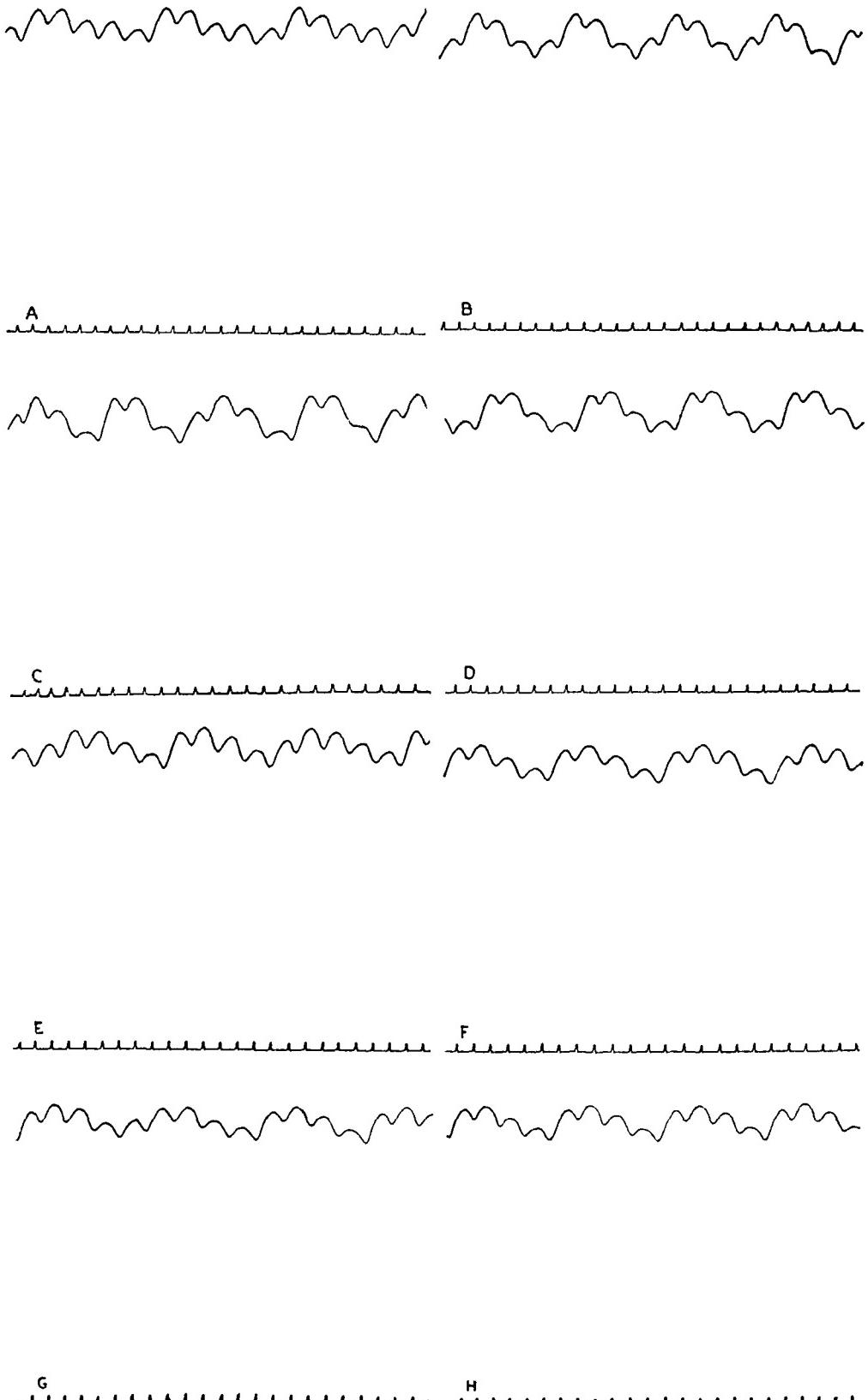


Fig 3.—Sections of blood pressure records from the carotid artery taken at points marked with marginal letters in Table 2. The serum injected was from a dog in the stage of morphin withdrawal. A-B represent normal records C-H represent the records after the injection. The record of the time marker indicates fifths of seconds and also serves as the zero base line for the blood pressure record.

ferent lines would be desirable, and next proceeded to electrocardiographic studies. By this procedure, we were enabled to dispense entirely with anesthesia and thus avoid any possible disturbing factor that might be due to the anesthetic. Moreover, it afforded a more sensitive means of testing the heart rate and rhythm.

In these studies, we exercised the greatest care. Our first step was a preliminary period of training of the dog, which was a female weighing

TABLE 3—*Effect of Normal Dog Serum*

	Time	Heart Rate per Min	Blood Pressure in Mm Hg	Remarks
(a)	4 05	160	118	Before injection
	4 10	168	120	Before injection
	4 15	162	117	Before injection
(b)	4 20	160	116	Before injection
	4 23 *	156	116	Injection of serum started
(c)	4 26 *	162	118	After 3 c.c. of serum
	4 29	165	122	After 6 c.c. of serum
(d)	4 31	168	124	After 9 c.c. of serum
	4 34	168	122	After 12 c.c. of serum
(e)	4 37	168	123	After 15 c.c. of serum
	4 40	171	123	After 18 c.c. of serum
(f)	4 43	171	121	After 21 c.c. of serum
	4 46	174	119	After 24 c.c. of serum
(g)	4 49	171	120	After 27 c.c. of serum
	4 51	174	122	After 30 c.c. of serum
(h)	4 54	174	122	After 33 c.c. of serum
	4 57	174	118	After 36 c.c. of serum
(i)	5 00	174	122	After 39 c.c. of serum
	5 03	174	120	After 42 c.c. of serum
(j)	5 06	177	122	After 45 c.c. of serum
	5 09	177	124	After 48 c.c. of serum
(k)	5 12	177	124	After 51 c.c. of serum
	5 15	180	124	After 54 c.c. of serum
(l)	5 18	183	122	After 57 c.c. of serum
	5 23	183	119	After 60 c.c. of serum
(m)	5 28	183	120	
	5 33	180	120	
(n)	5 38	177	126	
				Injection stopped
Blood Pressure in Mm Hg			Before Injection	After Injection
Highest			120	126
Lowest			116	116
			—	—
Heart Rate per Min			4	10
Highest			168	183
Lowest			160	156
			—	—
			8	27

ing 9 kg. This period covered three weeks. The training consisted in accustoming the dog to lie quietly on its side in a comfortable position in a room which was kept absolutely quiet, until it was able to maintain this position in perfect relaxation for about two hours at a time. The dog was kept warm by covering. After this stage of training had been reached, the electrodes and a respiration tambour were attached, and the dog was accustomed for a further period to these additional conditions. For several days before the actual experiments were started, slight skin incisions were made in the neck, simulating the exposing of the external jugular vein.

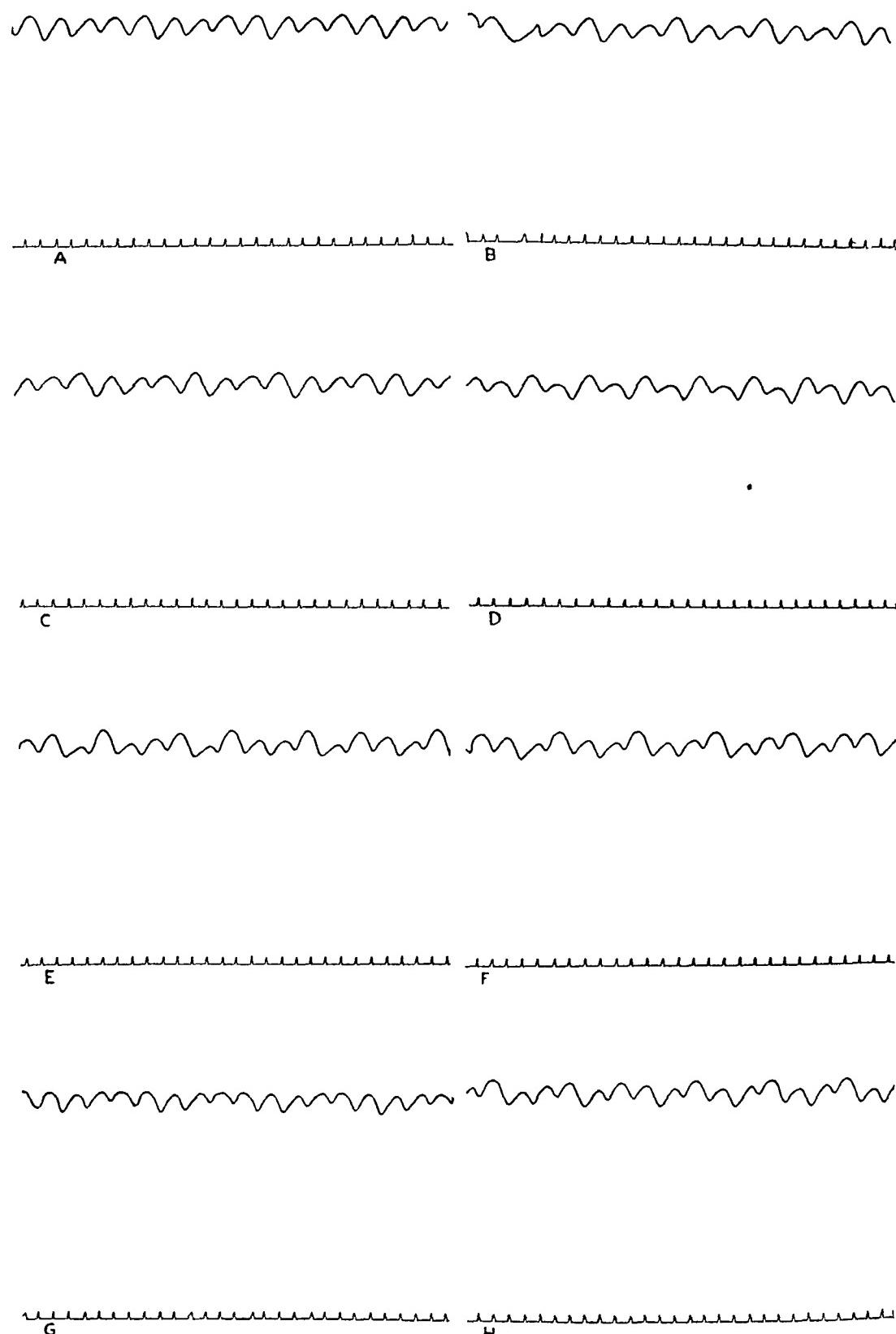


Fig 4.—Sections of blood pressure records from the carotid artery taken at points marked with marginal letters in Table 3. The serum injected was normal dog serum A-B records before injection C-H records after injection

In studying this dog, we took not only the electrocardiograms but also the respiratory tracings on the same film, synchronized as nearly as possible with the heart record. This was accomplished by attaching to the dog's chest a respiration tambour, connected by a rubber tubing to a recording tambour so placed that the lever moved across the aperture of the camera of the electrocardiographic apparatus. The latter was in a different room, some distance from that in which the dog was placed, to avoid disturbance by noise. In taking the electrocardiograms, we confined ourselves to the second lead throughout.

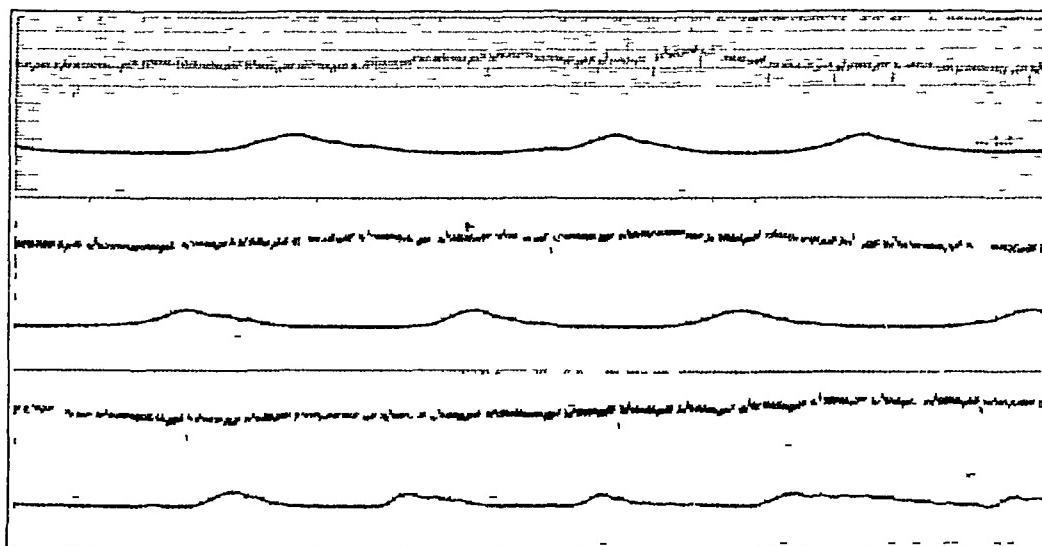


Fig 5.—Sections of electrocardiograms (second lead) of a normal dog from which Table 4 was compiled. The upper tracing in each record represents the respiratory cycle.

Our first experiment with this dog consisted in taking electrocardiograms under the above described conditions, without injection, to obtain a normal record. Table 4 shows the results of three electrocardiograms taken at five-minute intervals.

TABLE 4.—*Electrocardiographic Studies of Normal Dog*

No. of Film	Heart Rate per Min
31	102.5
32	97.7
33	90.3

In the accompanying electrocardiograms, it will be noted that the length of the individual complexes varies. On analysis, it appears that these variations occur regularly at definite intervals, and when compared with the tracing of the respiration it will be seen that there is a definite relationship between the rhythms of the respiration and the heart. It is clearly evident that the variation in heart rhythm is of

respiratory origin and must be discounted in estimating the effects of any injection. From our experience in electrocardiographic studies of other dogs, we have found that respiratory sinus arrhythmia is always present in the unanesthetized animal.

The next experiment on this dog, after an interval of five days, consisted in taking electrocardiograms with the injection of normal dog serum. The serum was kept warm during the injection, which was made into the external jugular vein, into which a cannula had been placed, without any evidence of pain or struggling on the part of the animal. Table 5 gives the results of this experiment.

TABLE 5—*Electrocardiographic Study of Effect of Normal Dog Serum*

No of Film	Time	Heart Rate per Min	Remarks
41	2 55	122 4	Before injection
42	3 00	117 0	Before injection
43	3 05	127 2	Before injection
			Injection started
44	3 09	120 8	After 10 c c serum
45	3 13	123 9	After 20 c c serum
46	3 17	115 2	After 30 c c serum
47	3 21	127 8	After 40 c c serum
48	3 25	110 2	After 50 c c serum
			Injection stopped
49	3 30	139 6	
410	3 35	131 8	
411	3 45	138 3	
Heart Rate per Min			
Highest		127 2	Before Injection
Lowest		117 0	After Injection
		10 2	139 6
			110 2
			29 4

Our final experiment with this dog, performed four days later, consisted in injecting, in place of normal serum, serum obtained from the blood drawn from the morphinized dog in withdrawal cited above, other conditions being identical with those of the preceding experiment. Table 6 shows the results of this experiment.

TABLE 6—*Electrocardiographic Study of Effect of Serum of Morphinized Dog in Withdrawal*

No of Film	Time	Heart Rate per Min	Remarks
51	4 40	102 3	Before injection
52	4 45	105 4	Before injection
53	4 50	80 0	Before injection
			Started injection
54	4 54	96 0	After 10 c c serum
55	4 58	87 4	After 20 c c serum
56	5 02	81 0	After 30 c c serum
57	5 06	88 8	After 40 c c serum
58	5 10	85 8	After 50 c c serum
			Injection stopped
59	5 15	72 8	
510	5 20	75 6	
511	5 30	86 6	
Heart Rate per Min			
Highest		105 4	Before Injection
Lowest		80 0	After Injection
		25 4	96 0
			72 8
			23 2

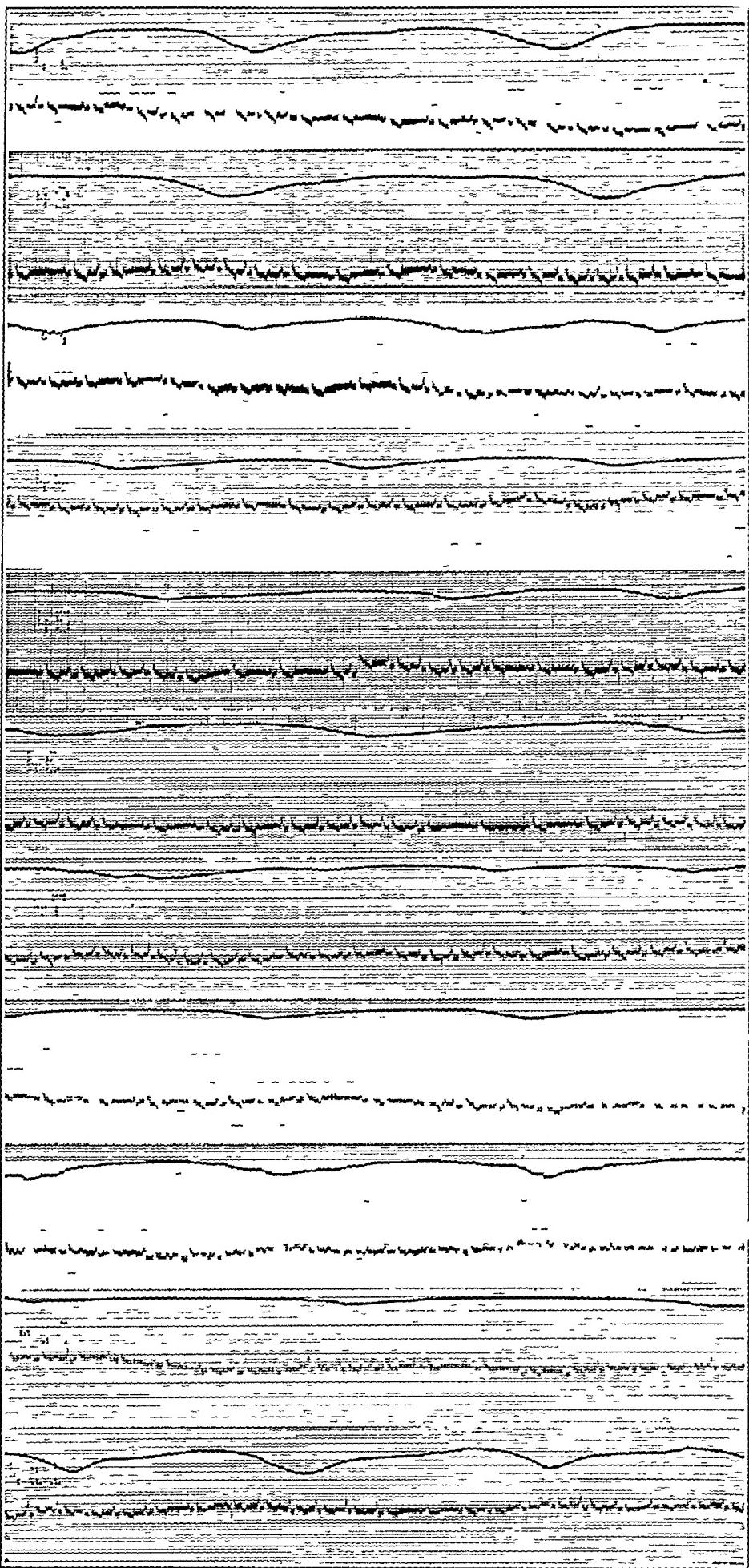


Fig 6.—Sections of electrocardiograms (second lead), showing the effect of normal dog serum, from which Table 5 was made

Comparison of these results with those of the preceding experiment shows no effects from the serum of the morphinized dog in withdrawal comparable to those shown by Valenti, thus confirming the results shown in Tables 2 and 3.

Besides studying changes in heart rate, the electrocardiograms were analyzed also for the maximum variations in the auricular complex, the ventricular complex, the complete cardiac diastole, the sequence and the rhythm of the heart. The results of the analysis did not show any effect that could be attributed to the serum of the morphinized dog in withdrawal and such variations as occurred were fully explained by respiratory sinus arrhythmia.

Since the foregoing experiments were confined to a study of possible effects on the circulation, we thought it desirable to extend the scope of our investigation to include other studies which might throw light on the effect of the serum, such as possible effects on the central

TABLE 7.—*Data Regarding Serums Used for Cat Experiments*

Experiment	Period of Addiction	Daily Dose of Morphin at Close of Period	Time of Drawing Blood After Withdrawal of Morphin
1	3 months	0.4 gm	2 days
2	6 months	0.9 gm	3 days
3	3 months	0.5 gm	2 days
4	10 months	2.75 gm	4½ hours
5	1 year	1.0 gm	3 days
6	1 year	1.0 gm	18 hours

nervous system or on the chemical composition of the blood. We therefore conducted, concurrently with our experiments on the circulation, two other series, in one of which we endeavored to ascertain by observation of the behavior and general symptoms of cats injected with such serum, whether any effects were produced, especially any referable to the central nervous system. Our technic in this series was as follows. The cats, which were not anesthetized, were placed in a box from which the head and neck alone projected, the external jugular vein was exposed just sufficiently to permit the insertion of a hypodermic needle, and 10 cc of serum was quickly injected by means of a syringe. The cat was then immediately released, the whole procedure described taking not more than three or four minutes. The animal was then kept under close observation for an hour or more, being allowed to roam at will in the laboratory. Six cats were injected with serum, and Table 7 gives data regarding the dog serum used in each case.

In all cases, the behavior of the cats was entirely normal, and they showed no effects from the injection of the serum.

Our final series consisted in analysis of the blood of morphinized dogs in withdrawal. The analysis of the blood was performed accord-

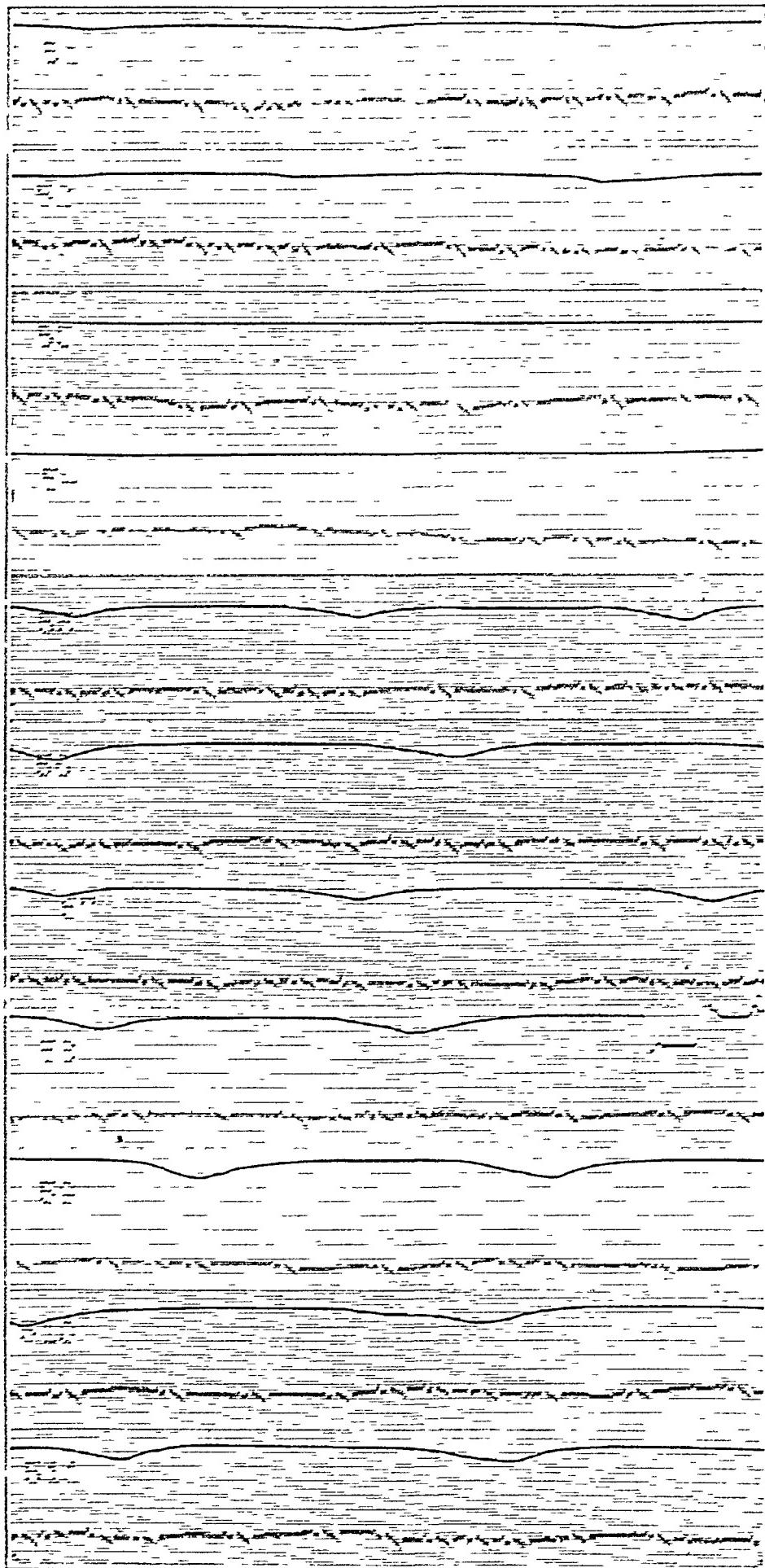


Fig. 7.—Sections of electrocardiograms (seconda lead) showing the effect of serum of morphinized dog withdrawn from which Table 6 was made

ing to the methods of Folin and Wu⁶ and of Van Slyke⁷. The blood used was obtained from the dogs and at the times described in Experiments, 2, 4, 5 and 6 of Table 7. Table 8 gives the results.

TABLE 8.—*Chemical Analysis of the Blood of Morphinized Dogs in Withdrawal*

	Dog 2, Mg	Dog 4, Mg	Dog 5, Mg	Dog 6, Mg
Nonprotein nitrogen	30.0	31.0	29.0	28.8
Urea	17.2	15.0	15.4	13.4
Creatinin	1.2	1.5	1.2	1.2
Uric Acid	1.0	1.0	2.3	2.0
Sugar	110.0	104.0	75.0	76.9
Whole blood chlorids	450.0	544.5	475.0	585.0
Carbon dioxide	52.2%	50.0%	52.0%	56.6%

The foregoing results are well within the range of normal dogs' blood.

COMMENT

Before comparing our results with those of Valenti, it may be desirable to make a few comments on his report. One of the features of his results to which he attaches great significance is the marked increase in range of variations in blood pressure and heart rate, after injection of the serum of a morphinized dog in withdrawal, as compared with the range in the normal period before injection. His method of obtaining this result from his records is to select the highest and lowest points, wherever they may occur in the normal period and in the period after starting the injection, respectively, and compare the differences. We find a few instances of errors made by him in the selection of these figures from his records (see Figures 1 and 2), but this does not affect the general nature of his results. In reporting that phase of our work, which was an attempt to duplicate his, we adopted the same method in order to permit of exact comparison, but we are unable to appreciate the significance of this particular feature of the results.

Examination of his tables shows that, in the majority of instances, the extreme high and low points of both the heart rate and blood pressure occur at various points in the progress of the experiment, and that both the heart rate and the blood pressure range up and down throughout the experiment, rather than following a definite and consistent course. It is hard to conceive of any substance which, when injected at a uniform rate into the veins of an animal, would be capable of producing such an irregular effect. Similar effects can be produced by substances which are rapidly absorbed and excreted, when not administered uniformly. It is well known that ether administration, when not under exact control, will produce these effects. It will be

6 Folin, O., and Wu, H. J. Biol. Chem. **38** 81 (May) 1919.

7 Van Slyke, D. D. J. Biol. Chem. **30** 347 (June) 1917.

noted that, as already stated, Valenti does not specify the form of anesthetic used in his experiments. It appears, however, that in his control experiments, using normal dog serum, he reports much smaller variations, and we are unable to offer any explanation of these observations. In our work, as will be seen from our tables, we obtained no results showing any substantial difference, as regards variability in heart rate or blood pressure, between the effects of the serum of a morphinized dog in withdrawal and those of normal dog serum. The slight differences occurring were more marked following the injection of normal serum.

Another feature of Valenti's reported results on which he lays much stress is the arrhythmia which he states is produced by the injection of the serum of a morphinized dog in withdrawal. We have given sections of his tracing which he selected as showing three different types of arrhythmia. We have also given sections of our tracings for comparison. Our results do not correspond with his, as the tracing of our experiment with such serum shows no arrhythmia. The variations of rhythm shown in our tracing of the dog injected with normal dog serum are of the type obviously associated with respiratory changes.

The electrocardiographic method is, of course, much better adapted to show these features of the heart action than the mercury manometer, and it is naturally to be expected that if arrhythmia were produced it would be plainly apparent in the electrocardiograms. Our electrocardiographic studies show no abnormal arrhythmia. Such changes in rhythm as appear are in the first place, uniform in all our electrocardiographic experiments, and, in the second place, clearly respiratory, as may be seen by comparison with the respiration curve. It is worthy of note that in the electrocardiographic experiments no anesthetic was used.

Valenti finds that the degree of circulatory disturbance produced by the injection of the serum of the morphinized dog in withdrawal is directly dependent on the total amount of morphin consumed during the addiction period. The largest total amount consumed by any of the dogs from which he obtained serum for injection was 69.95 gm. The serum in the experiments on the circulation presented by us was obtained from a dog that had received a total of 168.62 gm. If his conception is correct, our results should have been much more pronounced than his. The same reasoning applies in a measure to the question of the length of time of withdrawal of the morphin. While Valenti claims that the serum is equally effective when the blood is drawn at any time from thirty-six hours to twenty days after stoppage of morphin administration, we ascertained by electrocardiographic studies that there was a definite time at which the circulatory distur-

bances in the morphinized dog were at their maximum, and the serum used by us was obtained from blood drawn at that time⁸

We feel that our work on cats and blood analysis is corroborative of our negative findings. We also feel that the conclusions reported in our first paper of this series have a definite bearing on the question now under discussion. We there reported that the serum of morphin addicted dogs and humans had no protective effect against a minimal fatal dose of morphin. If there was any toxic substance in the blood causing circulatory changes, which, as Valenti claims, could be neutralized in its physiologic effects by the administration of morphin, it is difficult to conceive the nature of such substance unless it is either chemically or physiologically an antidote to morphin. Our previous work shows conclusively that no such substance is present.

A notable point in Valenti's report is the statement that the circulatory disturbances in morphinized dogs can be suppressed, and the normal circulatory condition restored, at any time from thirty-six hours to twenty-one days after withdrawal, by administration of the previously accustomed daily dose of morphin. He emphasizes the fact that this effect cannot be produced by any amount less than the previous daily dose, and that it is only when this amount is exceeded that the typical "morphin pulse" becomes evident. Such persistence of tolerance as he reports is directly contrary not only to the generally known facts in the case of human beings, but also to the results of careful experiments on animals by competent investigators. Cloetta,⁹ experimenting on rats and pigeons, found that these animals lost their tolerance as early as two days after the withdrawal and that the previous daily dose, if of a size fatal to a normal animal, proved fatal to these previously tolerant animals after this lapse of time. Van Egmond¹⁰ showed that in dogs accustomed to tolerate 1 gm of morphin daily the vagus center still responds to the injection of minute doses. He found it possible to change the heart rate from 120 to 80 per minute by a dose of 0.04 gm, while doses as small as 0.00008 gm per kilogram in these same animals showed an appreciable effect. Van Dongen¹¹ and Tamura¹² also found that the vagus center does not become tolerant to morphin. In the course of our work, we found that profound general effects were pro-

⁸ We expect to discuss this question of changes in heart rate of the morphinized dog in withdrawal in a subsequent article. We are prepared to say at this time that we are satisfied that these changes are not due to any toxic substance in the blood.

⁹ Cloetta Arch f exper Path u Pharmakol **50** 453, 1903

¹⁰ Van Egmond Arch f exper Path u Pharmakol **65** 197, 1911

¹¹ Van Dongen Arch f d ges Physiol **162** 54, 1915

¹² Tamura, O Physiol Abstracts **6** 525, 1921

duced by the injection, three days after the withdrawal, of a previous daily dose of 1 gm., and that these effects were noted very promptly, being quite pronounced within twenty minutes or less time.

We feel that Valenti's failure to give important details of his technic (e.g., the anesthetic used), the peculiar way in which he arrives at his conclusions by selection of figures from his records, and the impossibility of rationally reconciling his results with those of other workers who have investigated different aspects of the effects of morphin tolerance, and whose conclusions have met with general acceptance, lend weight to the conclusion to be drawn from the consistently negative results of our own work. We feel that our technic was such as to eliminate possible extraneous factors that may have influenced Valenti's results, and that the conditions under which our work was performed were even better calculated to obtain clear positive results from any toxic substance that might be present in the blood.

CONCLUSIONS

1 No toxic substance is formed in the blood of dogs habituated to morphin which is capable of producing circulatory disturbances in normal animals into which the serum is injected.

2 We find no evidence that any toxic substance is present in the blood as a result of morphin habituation.

CONGENITAL PERIPHERAL RESISTANCE, ITS CAUSATIVE RELATION TO THE PRECOCIOUS HYPERTENSIVE STATES *

ELI MOSCHCOWITZ, M.D.

NEW YORK

Until recently, hypertension was considered entirely the result of arterial and renal disease. Although the mechanism whereby such disease caused hypertension was unknown, the almost constant association of the symptom and such lesions seemed to justify such a conclusion. This was in accord with the still dominant tradition of the continental school, namely, that an abnormal function must necessarily be the result of a morphologic tissue change. It is becoming increasingly apparent, however, that an association of a lesion with a functional change does not always necessarily imply that this change is the result of the lesion. The lesion may represent an end-result of influences in which the functional change is the main or an important factor.

Correlation of pathologic evidence and clinical data furthermore revealed striking discrepancies. 1. Hypertension was present although at postmortem there was little evidence of arterial or vascular disease. Such cases are by no means rare. I reported five such, observed within a year.¹ 2. Renal and vascular disease, sometimes even marked, may be present, although the patient at no time had hypertension. Such cases may be said to be "normal" in patients past 55 years of age, these have been termed "decrecent arteriosclerosis and nephritis" by Clifford Allbutt.³ There is no relation whatever between the grade of the hypertension and the extent and gravity of the arterial or renal lesion. These are serious obstacles to a rational explanation of hypertension on a renal or vascular basis and have in recent years again made the problem of the cause of hypertension an open issue.

What then is the relation of hypertension to disease of the renal and vascular systems? Evidence is accumulating that such lesions are the result of the hypertension itself, or better said, of the normal intravascular tension. Hypertension, which is merely an exaggeration of the normal tension, brings about such lesions earlier than they otherwise would occur. "Decrement" lesions of kidneys and arteries are therefore the result of tension. The precocious and presenile lesions are the result of hypertension.

* From the Pathological Laboratory, Beth Israel Hospital, and the First Medical Division, Mount Sinai Hospital.

¹ Moschcowitz, Eli. Hypertension with Minimal Renal Lesions, J. A. M. A. 77: 1075 (Oct 1) 1921.

This is not the place to discuss the arguments for this thesis Those interested are referred to previous papers on this phase of the problem²

In this conception, hypertension is not a "symptom" but the disease itself In other words, function may not be interpreted in terms of anatomy, but reversely As a matter of fact, our observations have shown that the clinical concept known as "essential hypertension" represents the earliest phase of cardiovascular renal disease Conversely, most cases of arteriosclerosis and nephritis with hypertension at some time were cases of "essential hypertension"

Hypertension is a "disease" only on nosologic grounds As far as our present methods of study permit us, a morphologic background is still lacking Its genesis must be interpreted in terms of pathologic physiology rather than in those of anatomy

In such an interpretation, an increase in peripheral resistance is the most important factor in the maintenance of an increased blood pressure in the general vascular system Whether this resistance is in the peripheral portions of the arterial tree—the arterioles—as some aver, or in the capillaries, or whether the resistance is the result of functional or organic changes or both are problems that are as yet unanswerable

The problem is clearer in regard to the cause of arteriosclerosis within the pulmonary circulation Here, the peripheral resistance, in most instances, is a definite organic change, a stenosis of the mitral valve Less often the increased intrapulmonary tension is the result of emphysema, chronic asthma and bronchitis, and narrowing of the main pulmonary trunks due to severe kyphoscoliosis Arteriosclerosis of the pulmonary vessels and the associated lesion, which I have termed "arteriocapillary fibrosis" of the lung (Stauung's induration), a lesion analogous to arteriocapillary fibrosis of the kidney, practically never occurs unless such peripheral resistance is present²

The direct cause, then, of the increase in peripheral resistance in the greater circulation is obscure I have described³ a "type" patient, a combination of psychic and physical characters, in whom hypertension is apt to occur Such an individual may be best visualized as the antithesis of the child in psyche The stresses and strains of our civilization and the consequent strivings for "success" do much to bring this about

The physical characters of such individuals are partly hereditary and partly the result of the psychic makeup The latter is probably responsible for the overweight These people do not play or exercise How psychic influences cause persistent increase in peripheral influences

2 Moschcowitz, Eli Pathology of Hypertension, J A M A **79** 1196 (Oct 7) 1922

3 Moschcowitz, Eli Am J M Sc **158** 668 (Nov) 1919

is entirely speculative. We must know more of pathologic physiology of the blood vessels before this question can be answered.

In another group of cases, hypertension is the result of a persistent exophthalmic goiter. This is by no means an uncommon observation. It is well known that the tachycardia of exophthalmic goiter is associated with a normal or an elevated blood pressure. If the exophthalmic goiter persists over an extended period, the elevation of pressure may persist despite the eventual subsidence of other symptoms. In time, the classic evidences of clinical arteriosclerosis and nephritis develop. As the cause of exophthalmic goiter in most instances can be traced to emotional instability and psychic trauma, the relationship of psychic strain to hypertension cannot be lightly dismissed.

There, nevertheless, remains a large group of cases into which neither of these causes enter. We refer especially to cases of juvenile or presenile hypertension—cases in which hypertension occurs long before middle life, when hypertension is most commonly noted.

With the causes of pulmonary hypertension still in mind, the problem presented itself as involving an investigation into the possibility of an organic increased peripheral resistance in these cases. A clue was given in the following case.

In 1920, Dr. B. S. Oppenheimer, at a clinical conference of Mount Sinai Hospital, presented a boy, aged 15, suffering from coarctation of the aorta. All the classic evidences of this lesion were manifest, subjective, physical and roentgenologic. The anastomotic internal mammary, scapular and vertebral arteries were enormous and tortuous. But there were other significant signs and symptoms. The blood pressure was 180 systolic, the urine contained albumin and casts, the radials and anastomotic arteries were hard and extremely tortuous.

This patient, therefore, suggested the following problem. Was the hypertension the result of the increased peripheral resistance existing, by an anomaly of nature, in the isthmus of the aorta, and was the manifest arteriosclerosis and chronic nephritis sequential to the hypertension? Or was the association of the hypertension and the attendant lesions merely casual and without bearing on the coarctation?

As the rarity of coarctation of the aorta did not offer much prospect of immediate observation with these issues in view, a recourse to the literature on coarctation of the aorta was necessary. It soon became apparent that there were certain deficiencies in observation. 1. The vast majority of the observations antedate the discovery of the sphygmomanometer. 2. Either clinical data are insufficient or a precise morbid anatomy is wanting. Nevertheless, the mass of available data furnishes sufficient evidence to show that hypertension and the associated arteriosclerosis and nephritis are common sequelae to congenital narrowing of the aortic isthmus.

In 1872, Eppinger⁴ reported two cases. In the first, in a woman of 61, contracted kidneys were revealed at necropsy. In the second, in a youth, aged 17, who died of cerebral hemorrhages, the kidneys were "small, firm and tough."

In 1897, Schichold⁵ reported the case of a woman, aged 32, who since childhood suffered from dyspnea, palpitation, and edema of the legs. The temporal arteries were tortuous, the left ventricle was enlarged, and there was present an aortic insufficiency. At necropsy, the aortic valves were greatly thickened and covered with warty vegetations, the root of the aorta was much thickened. It revealed profound arteriosclerosis and was elongated. The findings in other organs are not mentioned.

In 1900, Schlesinger⁶ reported the case of a man, aged 50, with cardiac symptoms and the typical collateral circulation of the internal mammary arteries. The vertebra and the subscapular arteries were much "thickened and elongated."

In 1901, Minkowski⁷ reported a patient, aged 23, whose blood pressure was 300 (Riva-Rocci) and whose kidney function was normal.

In 1901, Bandel⁸ reported the case of a man, aged 19, whose blood pressure was normal. The aorta was profoundly sclerotic. The kidneys, grossly, showed only congestion.

In 1902, Reinitz⁹ reported two cases. 1 A man aged 34, suffered sudden death from apoplexy. The aorta was sclerotic, the right kidney was large and smooth, and revealed good markings (no microscopic examination). The left kidney was absent. 2 A man, aged 37, committed suicide. The aorta was sclerosed, more markedly below than above the isthmus. The condition of kidneys is not mentioned.

In 1903, Haberer¹⁰ reported the case of a woman, aged 47, in whom there was complete obliteration of the aorta. "The blood pressure was enormously increased." There was marked general arteriosclerosis, especially of the collateral vessels. The aortic valves were adherent. The kidneys showed parenchymatous degeneration.

In 1905, Fawcett¹¹ reported eighteen cases. Two were diagnosed as chronic nephritis, but a reading of the histories would justify the inclusion of a number of others, most of the cases were in young or middle aged persons. Arteriosclerosis, especially of the collaterals, was present in practically every case. The necropsy protocols on the kidney lesions are poorly presented and microscopic reports are lacking.

In 1907, Monckberg¹² reported a marked sclerosis of the aortic valves in a patient, aged 50, which he believed was the result of hypertension.

In 1918, Paillard¹³ reported the case of a youth, aged 17, with marked hypertension in upper extremities. There was no necropsy.

In 1919, Lommel¹⁴ reported the case of a woman, aged 38, in whom the collateral vessels were thickened and tortuous. The blood pressure was 190. There was no necropsy.

In 1920, Hart¹⁵ reported the case of a man, aged 42. There was no blood pressure determinations. The collaterals showed profound arteriosclerosis.

4 Eppinger Prag Vierteljahrsschr **112** 31, 1872

5 Schichold Munchen med Wchnschr **44** 1279, 1917

6 Schlesinger Internat Clinics **55** 140, 1900

7 Minkowski Munchen med Wchnschr **48** 1335, 1901

8 Bandel Deutsch Arch f klin Med **72** 381, 1901

9 Reinitz Inaug Dissert, Kiel, 1902

10 Haberer Ztschr f Heilk **4** 26, 1903

11 Fawcett Guy's Hosp Rep **59** 1, 1905

12 Monckberg Verhandl d Deutsch path Gesellschr **11** 224, 1907

13 Paillard Thése, Paris, 1918-1919

14 Lommel Med Klin **15** 892, 1919

15 Hart, C Med Klin **16** 1337 (Dec 26) 1920

In the same year, Moon¹⁶ reported the case of a boy, aged 11, with marked thickening and rigidity of the edges of the aortic valves, giving rise to regurgitation.

In 1921, Follet and Caille¹⁷ reported the case of a youth, aged 17, with hypertension in the arms and very low pressure in the legs.

In 1922, Edelmann¹⁸ reported the case of a man, aged 25, whose blood pressure was 195 systolic, 45 diastolic. The collateral vessels were thickened and tortuous. No necropsy was performed.

Lanbry and Morre,¹⁹ in 1916, reported the case of a man, aged 29, in whom "the blood pressure was high."

These citations, which include the majority of case reports furnishing the necessary data on this problem, indicate that hypertension, arteriosclerosis and nephritis are very frequent sequelae of congenital stenosis of the aorta. This is especially noteworthy, since the majority of these patients had not reached the period of middle age. All observers are agreed that sclerosis of the valves and of the aorta below the point of stenosis are constant findings and that the aortic ring is consequently often insufficient. Indeed, rupture of the aorta due to the increased tension is not an uncommon end (Huchard)²⁰. As further circumstantial evidence that hypertension must be commonly present is the fact that apoplexy is a common mode of death in this condition (Minowski,⁷ Brunner²¹).

One must not carry away the impression that every case of congenital stenosis of the aorta is followed by hypertension and its attendant pathologic phenomena. Cases have been reported in which hypertension was not present (Strassner²²). Patients with this anomaly have been known to live to an advanced age, in one case to the age of 92. A normal or low tension may be explainable in one or two ways: 1. A previously existent high blood pressure became low as the result of cardiac decompensation. 2. The peripheral resistance was equalized by an unusually rich anastomosis (internal mammary, intercostal, vertebral and subscapular arteries).

CONGENITAL NARROWING OF THE AORTA (AORTA ANGUSTA)

A disproportion between the quantity of blood and hypoplasia of the vascular system will give rise to an increased peripheral resistance.

The concept of congenital hypoplasia of the aorta was introduced by Virchow,²³ who associated this lesion with chlorosis. Since then, the

16 Moon, R O Lancet **1** 1314 (June 19) 1920

17 Follet and Caille Arch d mal du cœur **14** 207 (May) 1921

18 Edelmann, A., and Moron, R Wien Arch f inn Med **4** 1 (April) 1922

1916 19 Lanbry and Morre Bull et mem Soc med d hôp de Paris **40** 2237,

1916

20 Huchard Traites des maladies du cœur et l'aorte, Paris, 1908

21 Brunner Deutsch med Wchnschr **24** 794, 1898

22 Strassner Deutsch Arch f klin Med **95** 344, 1909

23 Virchow Ueber die Chlorose, Berlin, 1872

study of the narrow aorta has been rather extensive, and it has been noted with a variety of conditions e.g., phthisis status thymicolumphaticus, chlorosis acromegaly hypoplasia and hypertrophy of the heart pernicious anemia and purpura hemorrhagica. A study of the literature on narrow aorta leaves one rather confused. In the first place, there is no absolute criterion as to what constitutes a narrow aorta. Beneke,²⁴ for instance, in a series of 100 necropsies found a wide range. At a distance of 1 cm above the valve, the circumference varied between 58.8 and 31.0 mm, in the middle of the thoracic aorta, between 40.7 and 13.2 mm, and at a point 3 cm above the bifurcation, between 33.3 and 13.2 mm. He found the diameter larger in males than in females, and there was an approximate relationship to the height and age of the individual. Scheel's²⁵ figures are somewhat higher. For instance between the ages of 20 and 30, the circumference of the ascending aorta averages between 62 and 57 mm. On the other hand, Strassburger²⁶ and Suter²⁷ claim that the width of the aorta as measured postmortem is no criterion as to its carrying capacity during life. They hold that elasticity and distensibility of the coats vary widely and that a presumably narrow aorta may become sufficiently wide under the normal intravascular tension.

Furthermore the association of narrow aorta with some of the conditions above described has been questioned. Thus in a recent critique, Louise Kaufmann²⁸ doubts whether a narrow aorta has any pathologic significance whatever. Her material is rather limited, being confined to young and middle aged soldiers. She studied the association of narrow aorta with phthisis and status thymicolumphaticus, and found that such individuals possess aortas with diameters within the normal range. Her findings in status thymicolumphaticus are in conflict with most of the testimony of other able observers notably Stoerk²⁹ and Kolisko.³⁰

Whatever the significance of narrow aorta may be, the fact remains that (1) there exists a uniform relative diminution in size of the aorta from the root to the iliac bifurcation, (2) the size of the aorta is fairly uniform for the age and height of the individual, (3) an aorta may be regarded as definitely narrow when it is at least from 5 to 10 mm smaller at a point 1 cm above the root than the mean averages compiled from the Beneke, Scheel and Kaufmann tables.

24 Beneke J f Kinderkr 4 380 1871

25 Scheel Virchows Arch f Path Anat 191·135, 1908

26 Strassburger Frankfurt Ztschr f Path 3 283 1909

27 Suter Arch f exper Path u Pharmacol 39 289, 1897

28 Kaufmann Zur Frage der Aorta angusta, Jena 1919

29 Stoerk Zur Klinik der Lymphatismus, Berlin, 1913

30 Kolisko Quoted by Stoerk (Footnote 29)

It is conceivable that a narrow aorta may furnish sufficient peripheral resistance to cause hypertension and its consequences, arteriosclerosis and nephritis, and thus explain the genesis of hypertension in cases otherwise obscure, for instance, juvenile and precocious hypertension. The first young nephritic on whom we had occasion to perform a post-mortem examination gave, in a striking fashion, expected findings.

REPORT OF CASE

History—M. K., aged 42, a driver, whose family and past history was irrelevant, for two and a half weeks had felt weak. There were general malaise, dyspnea and a dry cough. Five days before, there was epistaxis which lasted four days. Nocturia was present.

Examination—The patient had sonorous and moist râles at both bases. The apex of the heart was not visible. Maximum intensity of the sounds was in the fifth space, $1\frac{1}{2}$ inches (37 cm) within the mammary line. The second aortic sound was accentuated. The sounds were regular, and there were no murmurs. The radial arteries were thickened. The urine contained a heavy trace of albumin and the specific gravity varied between 1.017 and 1.023. Hyaline and granular casts were present. The phenolsulphonephthalein output in two hours was 12 per cent. The quantity averaged around 25 ounces (750 cc). The blood pressure during his stay varied between 190 and 248 systolic and 130 and 160 diastolic. The blood chemistry tests on admission showed urea, 23.0 nonprotein nitrogen, 48.7, creatinin, 1.5, glucose, 0.105. These figures rose steadily until twelve days later, when the urea was 60.6, nonprotein nitrogen, 79.3, creatinin, 2.0, glucose, 0.15. The retina and optic disk were edematous, the margins were indistinct. The veins were dilated, the arteries thin and in places invisible. There were hemorrhages along the vessel and the disk.

Necropsy—The lungs showed an old healed pleural tuberculosis of the right apex. Both bases were intensely congested and slightly edematous, the remainder of the lungs otherwise showed passive congestion. The heart was very large. The left ventricle was enormously dilated. There was marked hypertrophy, and the aortic valve was slightly rigid. The mitral valve was normal. There were some atherosclerotic patches on the upper inner wall of the left ventricle. The muscle was firm and brownish red. The aorta was markedly sclerosed and inelastic. The right ventricle was dilated. The pulmonary artery was smooth. The liver which showed advanced change of the nutmeg type weighed 1,360 gm. The spleen weighed 68 gm and was slightly enlarged, firm and a deep purple. The pancreas was enlarged and firm. The left kidney weighed 89 gm, the right, 140 gm. The capsule stripped easily. The surface was markedly granular. On section, the appearance was mottled, the cortex was thin, and the markings were very poor. The blood vessels were prominent.

Diameters, of the vascular system. The ascending aorta, 1 cm above the ring, measured 42.7 mm, the thoracic aorta, 34.5 mm, the common iliac artery, 15.7 mm, celiac axis, 12.6 mm, splenic artery, 6.3 mm, renal artery, 12.6 mm, innominate artery, 22.0 mm, common carotid artery, 12.6 mm, pulmonary artery, 57.5 mm.

Anatomical diagnosis. Hypoplasia of the vascular system, chronic diffuse nephritis (arteriocapillary fibrosis), chronic congestion of the lungs with hypostasis, hypertrophy and dilatation of both ventricles and chronic congestion of the spleen were diagnosed.

Microscopic Examination—The heart showed hypertrophy of the muscle fibers. There was brown pigmentation of the heart muscle and slight interstitial myocarditis. The lungs showed chronic passive congestion, and the spleen showed chronic congestion. The kidneys presented a diffuse growth of connective tissue, especially in the cortex. The glomeruli were shrunken, many showing connective tissue transformation with hyalinization and occasional calcification. The Bowman capsules were slightly thickened. The tubules were deformed and in connective tissue areas were either absent or few and small. In other areas, they were numerous and enlarged (compensatory hyperplasia). The blood vessels were thickened and showed intimal hyperplasia and connective tissue thickening.

In the meantime, investigation revealed a surprisingly comprehensive literature dealing with this topic.

Virchow,²⁰ in 1872, was apparently the first to note the association of early arteriosclerosis and nephritis with narrow aorta, but credit is due to Lancereau³¹ and his pupils, Besancon³² and Mosgofian³³ for the introduction and systemic study of this conception.

Lancereaux believes that the majority of nephritides in the young and the so-called hereditary nephritides are the result of congenital aplasia of the vascular system. His description of the clinical picture corresponds precisely to that associated in our minds with nephritis with hypertension, and the necropsy findings likewise reveal contracted kidney. The kidneys are small (from 45 to 80 gm.) and granular, the capsule is adherent, and the cortex is thin and contains cysts. Microscopically, there is enormous connective tissue increase with sclerosis of the vessels and glomeruli. Many patients give a history of chlorosis, and present evidences of infantilism. It is interesting to note that, from the point of view of pathogenesis, Lancereaux, even in the eighties, believed that increased intravascular tension was the cause of the condition.

Besancon's discussion is in a similar vein. He reports nine cases, varying between the ages of 18 and 35, in the four cases in which measurements were made, the diameter of the aorta at the root was 44, 42, 52 and 42 mm. Mosgofian, again, covers practically similar ground and reports eight cases, the patients varying in ages between 17 and 37. Indeed, he asserts that these cases are by no means uncommon. Subsequent writers (Frantzel,³⁴ Luzet³⁵ Spitzer,³⁶ Chiaruttini³⁷ Moutard,

31 Lancereaux Gaz Med de Paris **7** 172, 1891, Lecons de Clinique Medicale Paris, 1894, Diction Encyclopedique des Sci Med Paris, 1875, p 196

32 Besancon D'une nephrite liee a l'aplasie arterielle, Paris, 1889

33 Mosgofian These, Paris, 1893

34 Frantzel Berl klin Wchnschr **25** 575, 1888

35 Luzet Arch gen de med, 1890, p 725

36 Spitzer Wien med Wchnschr **47** 1602, 1897

37 Chiaruttini Clin med Ital **38** 481, 1899

Martin and Bacalogene,³⁸ Burke,³⁹ Romberg⁴⁰ and Apelt⁴¹) report a considerable number of cases, but add practically nothing new to Lancereaux's observations. Approaching the era when blood pressure determinations become routine, Wolkow⁴² describes rigidity of the radial arteries in young individuals of the gracile chlorotic type, associated with hypertension and signs of cardiovascular-renal disease, who at necropsy presented a narrow aorta. Muller⁴³ describes war recruits with rigid arteries and a drop heart associated with a narrow aorta. The most recent paper is by Strauss,⁴⁴ who also found recruits in the second and third decades with high blood pressure, hypertrophy of the left ventricle, rigid arteries and a narrow aorta. He attempts a clinical explanation of the condition and believes that an otherwise unexplainable hypertrophy of the left ventricle with arteriosclerosis in a young individual is suggestive of the presence of a narrow aorta.

These citations certainly show that cardiorenal disease especially in the young is frequently associated with narrow aorta. It does not follow that every young patient with an unexplainable nephritis possesses a narrow aorta. A recent necropsy, in the case of a man, aged 20, with cardiovascular disease, showed, for instance, an aorta of normal dimensions. It was thought that a perusal of the literature on hypertensive nephritis in childhood would afford corroboration of our thesis, but aside from some suggestive data, this proved unsatisfactory for the reason that the size of the aorta is ignored. Barlow⁴⁵ and Brault⁴⁶ mention the small size of the vessels in their cases of juvenile arteriosclerosis.

In this connection, certain observations in juvenile nephritis are significant as an indication that a maldevelopment of a hypoplastic nature is a factor in the condition. This may also explain cases of familial nephritis. Brill and Libman⁴⁷ report the case of a child of 14 with interstitial nephritis and arteriosclerosis, who was weak and undersized. The other children in the family had nephritis. Miller and Parsons⁴⁸ report cases of interstitial nephritis in children who presented a general aplasia. One child, aged 9, was the same size as his brother, aged 3.

38 Moutard, Martin and Bacalogene Bull et mem Soc med d hop de Paris **15** 110, 1898

39 Burke Deutsch Arch f klin Med **71** 189, 1901

40 Romberg Lehrb des Krankheiten des Herzens u Blutgefasse, Berlin, 1906

41 Apelt Deutsch med Wchnschr **31** 1186, 1905

42 Wolkow Verhandl Kong f inn Med **27** 611, 1910

43 Muller Med Klin **11** 1365, 1915

44 Strauss Med Klin **12** 416

45 Barlow Lancet **2** 151, 1874

46 Brault Arterites et Scleroses, Paris, 1897

47 Brill and Libman J Exper Med **4** 541, 1899

48 Miller and Parsons Brit J Dis Child **9** 289, 1912

He calls the condition "renal infantilism" Barker⁴⁹ reports two cases in the same family, both in children much undersized He subscribes to the previously mentioned conception of "renal infantilism" Hill⁵⁰ reports a case of chronic interstitial nephritis with hypertension in a child with infantilism

In a recent paper, Evans⁵¹ reports four cases of arteriosclerosis in children, all suffering from hypoplasia The familial tendency of juvenile arteriosclerosis and nephritis is commented on by most observers These evidences, while few, are suggestive, and the deficiencies in our observations are only too evident

Much work is necessary on the problem of juvenile or presenile arteriosclerosis and nephritis along the lines suggested in this paper before we can attain a correct knowledge of the statistical relationship of congenital peripheral resistances to hypertension and its sequences, arteriosclerosis and nephritis

CONCLUSIONS

- 1 The immediate cause of hypertension is unknown
- 2 Among the remote causes, psychic factors play an important rôle Evidence of this is presented in two varieties of individuals in whom hypertension is a common occurrence (a) the "type" individual described in a previous paper, who may be summarized as the antithesis of the "child" in makeup and temperament, (b) patients with the incomplete or complete forms of exophthalmic goiter or "autonomic imbalance" in whom accumulating evidence shows that psychic and emotional factors are of importance in their causation
- 3 Peripheral resistance is of importance in the causation of hypertension and its consequences, arteriosclerosis and nephritis In the lesser circulation, this is proved by the fact that, in cases of mitral stenosis, even in young individuals, marked arteriosclerosis of the pulmonary vessels and "arterio-capillary fibrosis" (Stauungs' induration) of the lung are present, while the systemic arteries in cases of general vascular hypertension show arteriosclerosis, the pulmonary vessels are free
- 4 There is evidence that a congenital peripheral resistance, either in the form of congenital stenosis of the isthmus of the aorta or a congenital narrow aorta (aorta angusta), may be the cause of hypertension, arteriosclerosis and nephritis This may account for the etiology of some cases of juvenile or presenile arteriosclerosis and nephritis and some cases of familial nephritis

49 Barker Brit M J 2 1204, 1913

50 Hill, L W Nephritis of Children, Am J Dis Child 17 270 (April) 1919

51 Evans, G Quart J Med 16 33 (Oct.) 1922

THE METABOLISM-PULSE RATIO IN EXOPHTHALMIC GOITER AND IN LEUKEMIA

WITH REMARKS ON CERTAIN SIMILARITIES IN THE SYMPTOMATOLOGY OF THESE DISEASES *

GEORGE RICHARDS MINOT, M.D.

AND

JAMES HOWARD MEANS, M.D.

WITH THE ASSISTANCE OF CONSTANCE HOPKINS

BOSTON

Experiment, as shown by Galen, consists of "putting questions to Nature and arranging matters so that Nature may answer them" The question we have asked is What causes the rapid pulse in hyperthyroidism? Is it dependent solely on the increased metabolic rate or is there invariably some other factor that produces tachycardia?

This question cannot be answered directly However, it occurred to us that light might be thrown on the subject by a comparison of the relation between basal metabolism and basal pulse rate in hyperthyroidism with that in leukemia These are the two afebrile¹ morbid states that are conspicuously characterized by an increased rate of heat production

For the purpose of comparison, a plot has been made of the basal metabolism rate (ordinates) against basal pulse rate (abscissae) for 180 observations in 126 cases of exophthalmic goiter (Chart 1) and for 110 observations² in seventy-one cases of chronic leukemia (Chart 2) Of the latter patients, forty-five had myelogenous and twenty-six lymphatic leukemia³ A similar comparison has been made by Sturgis⁴ in exophthalmic goiter, with results similar to those

* From the Medical Services of the Massachusetts General Hospital and the Collis P Huntington Hospital of Harvard University This paper is No 8 of a series of studies in metabolism from the Harvard Medical School and allied hospitals The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases

1 Fever of course occasionally occurs in leukemia, especially when the disease is very active Under such circumstances, a metabolic rate increment due to fever is probably superimposed upon that due to the disease per se

2 We are indebted to Dr James Hitchcock for making some of the determinations

3 No difference in ratio was found in the two forms of chronic leukemia

4 Sturgis, C C, and Tompkins, E H A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, Arch Int Med 26 467 (Oct) 1920

recorded below. Our observations were all taken when the patients had no fever. The basal pulse and basal metabolism observations represented by each point were simultaneous; when more than one observation was used in a given case, they were obtained on different days, usually some weeks apart. The results are shown in Charts 1 and 2. The general distribution of the dots is similar in the two. The distribution, however, at first appeared to be so wide that some doubt was had as to the propriety of drawing any conclusion from the data. They were therefore submitted for statistical study to Dr. W. T.

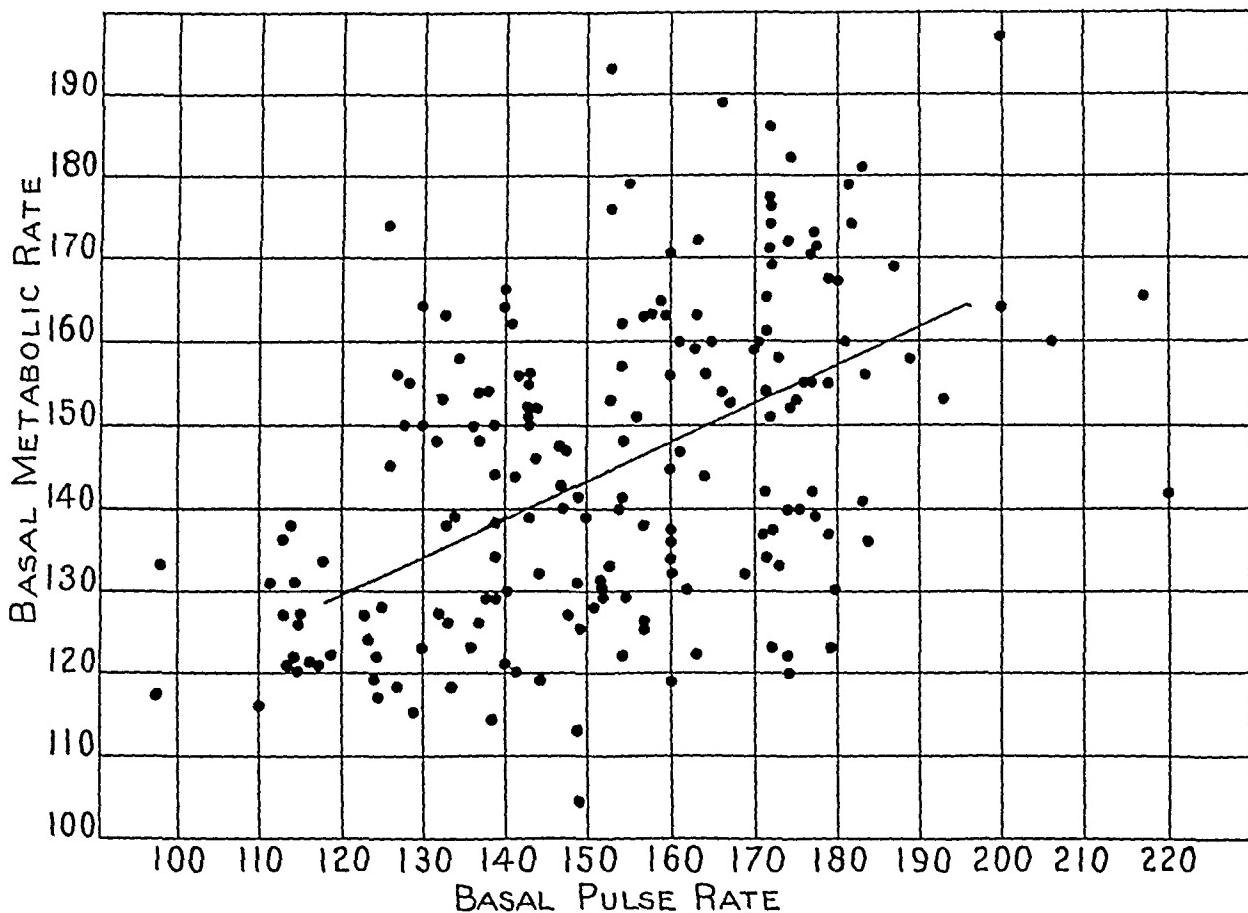


Chart 1—Exophthalmic goiter. In this and in Chart 2, the basal metabolic rate is plotted against the basal pulse rate. For convenience in the two charts, the basal pulse rate is expressed in percentage of normal as is the metabolism, instead of as beats per minute. The rate of 60 per minute was taken as normal for men, 70 for women, and each expressed as 100 per cent. The normal basal metabolic rate is also expressed as 100 per cent. The diagonal line is a smoothed curve representing the average distance of the dots above the base line.

Bovie, who found that there was a high degree of correlation between the data for basal pulse and basal metabolism in both diseases, the correlation coefficient in exophthalmic goiter being 0.525 ± 0.036 and in leukemia 0.544 ± 0.044 . Furthermore, the ratios in the two diseases were essentially the same. A smoothed curve representing the average

height above the base line is shown in each chart. This is of necessity at best only an approximation, but the similarity in the slopes of the two is striking.

These observations indicate that, for a given basal metabolic rate increase, there is about the same degree of pulse elevation in chronic leukemia as there is in exophthalmic goiter. In hyperthyroidism, certain circulatory abnormalities are regarded as cardinal symptoms of the disease; in leukemia, they are not generally so regarded. If the tachycardia of leukemia is purely a resultant of increased metabolic

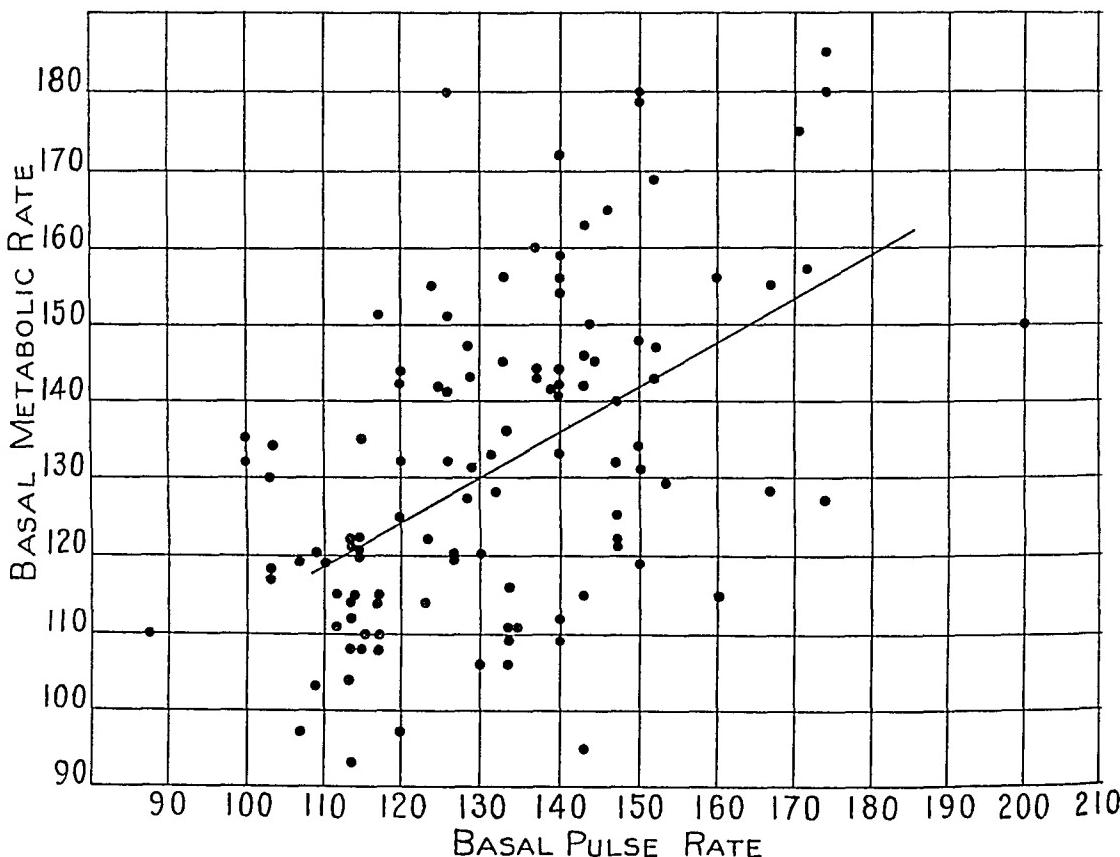


Chart 2.—Chronic Myelogenous and Lymphatic Leukemia

rate, that of exophthalmic goiter may well be considered as due to the same cause. We do not wish to imply that there never is any extra-metabolic factor in the production of the increased pulse rate of hyperthyroidism or leukemia. It is well recognized that there often is cardiac damage in hyperthyroidism of sufficient degree to be undoubtedly capable of increasing the tachycardia, while in leukemia, anemia may do the same. Anemia may also give rise to some degree of cardiac insufficiency. Even so, we believe it is a reasonable conclusion from the data given that, in the majority of uncomplicated cases of exoph-

thalmic goiter the increased metabolism is at least sufficient to account for the tachycardia observed. This conclusion is permissible provided the assumption is sound that there is no frequent important cardiac factor in leukemia. The rareness of cardiac insufficiency in the latter disease except as a late manifestation associated with profound anemia, suggests that this is so. Some cardiac enlargement in exophthalmic goiter is not infrequent⁵ and from our observations of fifteen cases it appears that the hearts of persons dying from leukemia are on the average 75 gm overweight. A similar condition is found in persons who have suffered from anemia for years⁶. Such cardiac hypertrophy presumably results from the long continued overwork by the heart and is not to be regarded as the primary cause of the tachycardia.

The symptomatology of the hyperthyroidism is peculiarly interesting, in that as pointed out by Du Bois,⁷ it can largely be explained on the basis of the known functional pathology. The increased rate of heat production together with an essentially normal body temperature directly explains the sensation of warmth, the increased sweating and the flushed moist skin, these being due to increased heat elimination. The loss of weight is a direct expression of increased heat production, and the excessive appetite an attempt on the part of the organism to compensate for this. The tachycardia as stated above may result from increased metabolism alone. The dyspnea in hyperthyroidism can also probably be explained without assumption of a primary cardiac factor. Certain of the nervous system symptoms such as irritability, tremor and asthenia and such symptoms as the eye signs, diarrhea and menstrual disturbances cannot be directly explained on the basis of increased metabolism. They may occur as noted by Kessel and Hyman⁸ in persons with normal metabolic rates as may neurogenic tachycardia also.

If the first category of symptoms given is in hyperthyroidism, a direct expression of increased heat production then in leukemia, even when afebrile one would expect to find these same symptoms. Statistical data concerning these symptoms in leukemia are at present not available but are in the process of compilation. However it is evident

⁵ Willis F A, and Boothby W M, with a note on the pathology by Wilson L B. The Heart in Exophthalmic Goiter and Adenoma with Hyperthyroidism. *Med Clinics N America* 7 189 (July) 1923

⁶ Cabot R C, and Richardson, O. Cardiac Hypertrophy in Pernicious Anemia. *J A M A* 72 991 (April 5) 1919

⁷ Du Bois E F. Metabolism in Exophthalmic Goiter, *Arch Int Med* 17 915 (June) 1916

⁸ Kessel Leo and Hyman H T. Studies of Graves Syndrome and Involuntary Nervous System Clinical Manifestations of Disturbances of Involuntary Nervous System (Autonomic Imbalance), *Am J M Sc* 165 513 (April) 1923

from the literature,⁹ as well as from our study of leukemia, that many of these symptoms are commonly observed in this disease. Leukemic patients quite constantly experience a sensation of warmth and show a distinct tolerance for cold in spite of anemia and emaciation. Increased sweating is not uncommon, a warm moist skin is often observed, and hot moist hands characteristic of exophthalmic goiter are not infrequent in leukemia. Flushing seems much less usual than in hyperthyroidism. Loss of weight, which often is marked and rapid, is a feature of leukemia, and many of these patients without gastro-intestinal complications have an increased desire for food. Dyspnea is common in both diseases, and while in leukemia, anemia plays a part, the increased metabolic rate in the two would seem to be an important factor in its production.

Nervousness, irritability, insomnia and tremor, symptoms of hyperthyroidism that are probably not directly due to increased metabolic rate, are not common in leukemia. The three former symptoms may occur in leukemia as in other chronic diseases, while we have observed occasionally a slight fine tremor when the disease is advanced and the hemoglobin considerably reduced. The eye signs observed in exophthalmic goiter are lacking in leukemia, though, as a great rarity, unilateral exophthalmos has been observed presumably due to leukemic infiltration or hemorrhage into the orbit. Persistent diarrhea does occur in leukemia, and not infrequently when many immature cells appear in the circulation. Menstrual irregularities may occur but are not prominent. Lack of strength or a sense of undue fatigue is one of the commonest symptoms to indicate to the patient with leukemia his ill health. However, it is more a lack of strength than a true myasthenia as seen in hyperthyroidism.

CONCLUSIONS

1 The amount of pulse elevation for a given metabolic rate elevation is essentially the same in hyperthyroidism and in chronic leukemia. From this, it is inferred that in both diseases the tachycardia is chiefly the result of an increased metabolic rate.

2 Certain symptoms of hyperthyroidism which are believed to be the direct expression of an increased metabolic rate also occur in leukemia, a disease likewise invariably characterized by increased heat production.

9 Ordway, T., and Gorham, L. W. Leukemia, The Oxford Medicine 2 681, New York, Oxford University Press, 1920 Vogel, K. M. The Leukemias, Nelson Loose-Leaf Medicine 4 66, New York, T. Nelson and Sons, 1920 Cabot, R. C. Leukemia, Osler and McCrae's Modern Medicine 4 659, Philadelphia, Lea and Febiger, 1915 Naegeli, O. Leukamien Blutkrankheiten und Blutdiagnostik, Lepsic, Veit and Company, 1912

AN ANATOMIC AND CHEMICAL REPORT ON A UNIQUE CASE OF MYELOMA¹

A. W. MEYER, MD AND F. A. CAJORI, MD
STANFORD UNIVERSITY, CALIF.

A careful scrutiny of the literature shows that only about seventy-seven cases of multiple myeloma have been reported to date (January, 1922). Eight of these were reported from Maryland alone. The two reported from California were observed in this laboratory. I may add that I know of a third case which occurred in one of the hospitals for the insane in this state. That the total number of cases observed is still small is shown also by the fact that Kahn² estimated that only sixty-one cases had been reported in 1914. The rareness of this condition would seem to be further emphasized by the fact that Symmers and Vance³ (1918) found only three cases among 2000 necropsies at Bellevue Hospital. It should be mentioned that Vance³ (1916) verified ninety-eight references on myeloma but that does not imply that the articles concerned the same number of cases. It is true that a single article sometimes covers several cases, but the reverse also happens. Hence it would seem that even the anatomist should not consign an incidental discovery of a case to oblivion especially not when as in the case reported here the anatomic findings are unique in at least two respects. Furthermore if attention is called to every additional case, a smaller number will be overlooked or go unrecorded in the future. Had attention been directed to the possibility of the existence of this condition, the cases reported from this laboratory would have been detected by clinicians. Either case could easily have been recognized positively by a roentgen-ray examination months before death. Perhaps it should be said that according to Beck and McCleary⁴ (1919), "roentgenologically no definite bone changes were demonstrable when their patient was first seen." Since swellings in both clavicles and one in the first rib said to have measured 5 cm in diameter were present, this statement is very perplexing. Pepper and Pearce⁵ (1917) also stated

¹ Anatomic report by Dr. Meyer Chemical by Dr. Cajori.

² Kahn, H. J. Four Cases of Multiple Myeloma, Med Rec 85, 1914.

³ Symmers Douglas and Vance M. Multiple Intravascular Hemangioendothelioma of Osseous Systems with Systems of Multiple Myeloma, Am. J. M. Sc. 152: 23 (July, 1916).

⁴ Beck, H. G. and McCleary S. Multiple Myelomas "in Bone Marrow Plasma Cells in the Blood. Report of Case J. A. M. A. 72: 490 (Feb. 15) 1919.

⁵ Pepper, O. H. P. and Pearce, R. M. Myeloma with Metastasis to Liver and Spine J. M. Research Post. 37: 171-182 (Sept.) 1917. Proc. Path Soc Phila 38.11 1918.

that the roentgen ray did not reveal the presence of osseous lesions in their case, although the compacta was only 0.5 mm thick and the pelvis, vertebrae and ribs were all involved by the disease. Failure of the roentgen ray to reveal the disease was attributed to its very diffuse form by these investigators. While this no doubt is an important factor, it would seem that, even when present in very diffuse form, the great thinning of the compacta which the disease sometimes effects should become evident in the roentgenograms as in the present cases and in Turner's⁶ (1921) cases.

A perusal of the later literature seems to indicate that there is an increase in the number of cases showing the presence of extraskeletal lesions. It must be clear, however, that if we are to regard the myelomatous condition as myeloblastic in origin, tumors in the kidneys, muscles, liver, fat, ovaries, lymph nodes, tonsils, etc., must be regarded as true metastases. Symmers and Vance regarded their Case 2 and that of Christian⁷ (1907) as the only cases with true metastases. Since then, other cases have been reported, and Pepper and Pearce⁵ discussed fifteen cases of probable metastases, only eight of which they regarded as doubtful. Morse⁸ (1920) also reported a case with metastases.

The probable duration of the disease was lengthened by reports on later cases, and pain seems to be given more prominence as an early symptom. Dyspnea or a hacking cough are more commonly mentioned. Arteriosclerosis seems to have been present in pronounced form in a number of cases, some of which, as those of Meyer and Swain⁹ (1918) and Beck and McCleary, also showed dilatation of the aortic arch. Since calcium phosphate is not infrequently deposited even in very large layers, in multiple myeloma, the presence of calcification in the vessels might really be expected to be more common than reported.

The clavicles seem to be affected with unusual frequency, and the roentgen ray is making it evident that one may speak of the disease as myelomatous even when it is very diffuse. This is well illustrated by the present case, in which it was difficult, if not impossible, to deliver any separate tumor mass completely. Yet as shown by the roentgenogram of the sternum, innumerable distinct tumors were present, making the photograph of the sternum look as though it contained innumerable bubbles.

6 Turner, W G Myeloma of the Vertebrae, *J Orth & Surg* 3 698 (Dec.) 1921

7 Christian, H A A Multiple Myeloma, *J Exper Med* 9, 1907

8 Morse, P F Peroxidase Reaction in Three Cases of Multiple Myeloma of Bones, with Remarks Concerning the Nosological Position of These Tumors, *J Cancer Research* 5 345 (Oct.) 1920

9 Meyer, A W, and Swain, R E Side-Lights on Multiple Myeloma, *Am J M Sc* 156 329 (Sept.) 1918

Both this case and the one previously reported (Meyer and Swain) presented a history of syphilis and arthritis and showed numerous fractures, fairly marked scleroses, calcareous deposits and evidences of periostitis in the form of roughenings of the external surface of a number of bones. The spleen was very small in the present case, weighing only 16.4 gm., and the uniqueness of the case lay in the peculiar deposits in many of the articular cartilages and the extensive urate deposits in the subcutaneous tissues and in some of the injured tendons.

REPORT OF CASE

A cigar maker and wood carver, aged 68, died of bronchopneumonia. In the clinical diagnosis, the presence of arteriosclerosis, bronchial asthma and chronic hypertrophic arthritis were noted. It probably is significant that 3 per cent of albumin was present in the urine and possibly also that the patient stated that he had had "sciatica" all over his body for years. His chief complaint on admission was shortness of breath on exertion, the duration of which he could not recall. The arthritis deformans was said to have begun fourteen years before.

COMMENT

In view of this fact, this period may also have been the duration of the myelomatous condition, especially so since the patient stated that he had sciatica all over for years. Multiple myeloma is assumed to run a rapid course, the usual duration, according to Nonne¹¹ (1921) being only one and one-half to two years and the longest duration on record being that of Graves' case, with a history of six years. According to Hirschfeld¹² (1920), the case of Kahler had a duration of eight years. Since the deformities in the hands, which were responsible for the diagnosis of arthritis deformans in this case, very evidently were due to the myelomatous condition, a long duration would seem very probable.

In view of the fact that the deforming deposits in the subcutaneous tissues of the fingers were urates it does not seem unlikely that these deposits had their origin in the extensive destruction of tissues necessarily accompanying multiple myeloma. Although it should be remembered in this connection that, in the case of Beck and McCleary, tophi were present in the ears, and a diagnosis of chronic gout was made. One cannot exclude the coexistence of gout in the present case, although such a diagnosis was not established clinically.

On inspection of the cadaver before dissection, large pigmented areas resembling scars in the anterior tibial regions were noted. A pronounced anterior curvature was present in the right tibia. This the history recorded as probably being congenital. The nodular irregularities in the right clavicle suggested

¹¹ Nonne M.: Beitrag zur Klinik der Myelom Erkrankung. Arch. f. Dermat. u. Syph. 132, 1921.

¹² Hirschfeld Hans: Das Myelom. Spezielle Pathologie und Therapie innerer Krankheiten. Vol. 8 Berlin, Wien, Kraus-Burgsch. 1921.

that the latter had been fractured twice, and a similar nodule in the left clavicle suggested that it also had been fractured. The most striking thing about the cadaver was the marked deformity of the hands, shown in Figure 1. The appearance of these deformities seemed to confirm the presence of *arthritis deformans* recorded in the history.

The entire cadaver looked decidedly senile and rather emaciated. Because of its apparent age and the fact that almost two years had elapsed since the patient died, no special significance was, at first, attached to the fact that all the ribs had been fractured in transportation by external pressures on the ventral surface of the thorax and that the left posterior parietal region of



Fig 1.—A, dorsal view of the intact left hand, B, dorsal view of the right hand with the skin removed

the skull was depressed. These things might have been due to postmortem injury. It seemed strange, however, that the ribs were so extremely pliable and that the sternum and calvarium yielded very easily to pressure. But since senile absorption not infrequently is very pronounced in these bones, this lack of usual resistance received no further attention, as the clinical history was not known at that time. It is significant in this connection that tenderness to thoracic pressure had been noted in the clinical history.

As soon as the scalp had been dissected, it was found that the entire calvarium was mottled, as shown in Figure 2, and that only a very thin plate of compacta remained in most of the affected regions. Closer examination showed that

the thin layers of bone overlying the darkened areas beneath were largely decalcified and that slight pressure caused them to yield.

Since the appearance of the calvarium was characteristic, and particularly since we had previously met with a case of multiple myeloma in the dissecting room, this disease naturally came to mind although no mention had been made of it in the clinical history. The surmise that this was a case of myeloma was confirmed by a reexamination of the places of fracture in the clavicles, and particularly by the extraordinary condition of the ribs and sternum. Further examination of the hands also revealed the fact that some of the nodules on the fingers were superficial and movable, and hence were deposits

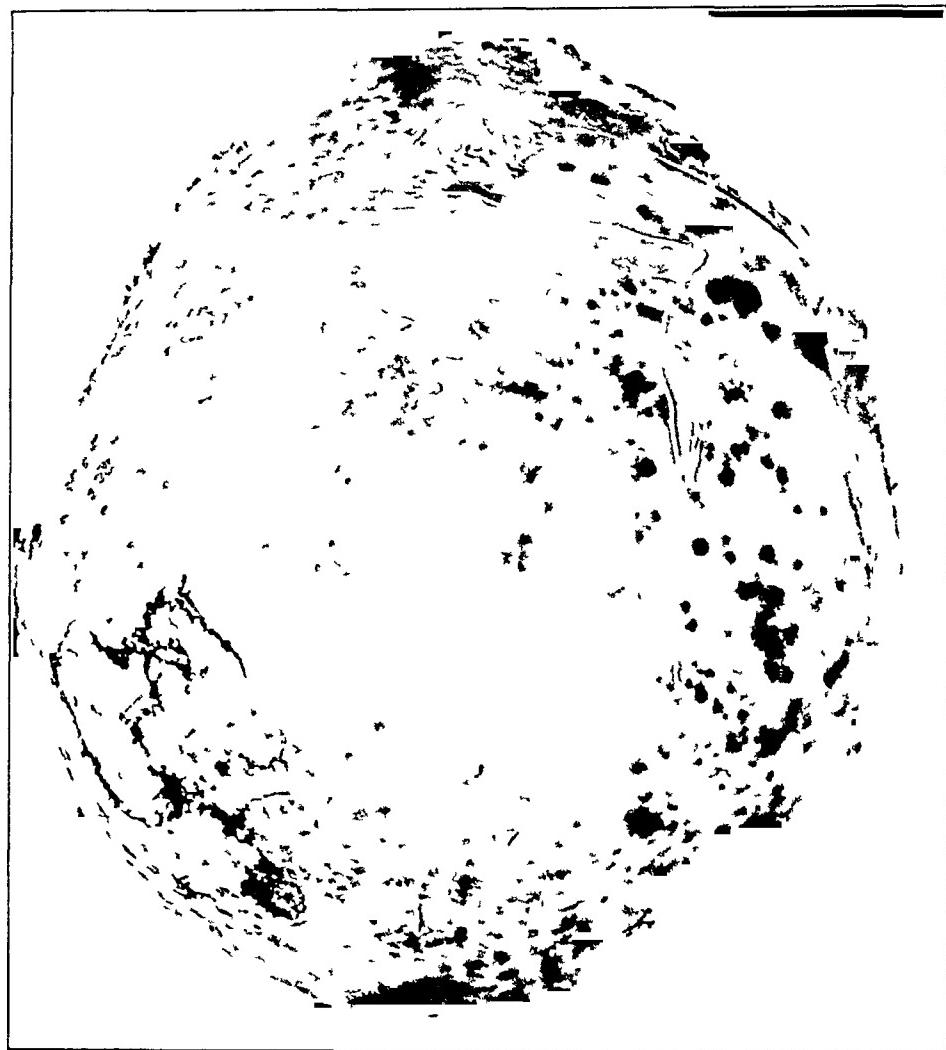


Fig. 2.—Calvarium, showing the numerous tumors

instead of osseous deformities due to arthritic changes. This inference was confirmed by further dissection, for even the large deposit on the dorsolateral surface of the medial phalanx of the third finger of the right hand could be easily removed from the underlying tendons and periosteum without damaging them. This was true also of the pronounced deposits responsible for the major part of the deformity at the distal interphalangeal joint of the same finger of the left hand.

The appearance of the larger calcium deposit is shown in section in Figure 3. This deposit measured approximately 2.5 by 1.5 by 1 cm. All these deposits were quite friable and largely devoid of tissue, and offered no special resistance.

to the edge of the knife. Their texture and appearance suggested calcium Tophi were not present, and nothing else directed attention to the possible existence of gout.

The gross examination of the calvarium showed that it was impossible to enucleate any of the tumors because they were insufficiently well delimited and too friable. This was quite in contrast to the case reported by Meyer and Swain. The tumors in the latter case were definitely delimited and could easily be removed intact after stripping of the periosteum.

As Figure 2 shows, most of the areas in which the myelomas had almost penetrated the external table of the calvarium were relatively small, ranging from pin-point size to approximately 1 cm in diameter. However, in the right frontal region there was one much larger area, measuring 3.5 cm in diameter. Here, the tumor was overlaid only by a thin plate of largely decalcified compacta. The destruction of bone seems to have been particularly complete in this area. The myelomas were so generally distributed throughout the calvarium that it was difficult to remove any of them without breaking the skull, and on

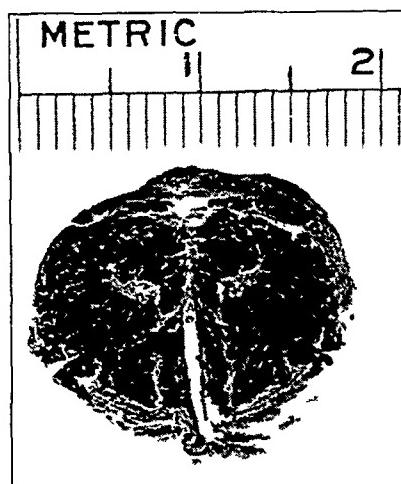


Fig. 3.—Large deposit from the dorsolateral interphalangeal region of the third finger of the right hand, in cross section, $\times 2$

attempting to detach the dura mater, it was found impossible to do so without running the risk of seriously damaging the calvarium or the base of the skull. Yet none of the tumor areas projected beyond the level of the calvarium either externally or internally. The dura was tightly adherent and somewhat thickened, but this was not the case with the pericranium, although it, too, seemed more closely adherent than usual. An inspection of the interior of the rest of the cranial cavity, especially of the base of the skull, showed that this was similarly, although not quite so generally, affected. The mandible showed no evidence of lesions on external inspection of the face before dissection.

The appearance of the exterior of the calvarium suggested that the tumors probably were disseminated throughout the entire diploe, and this surmise was confirmed by a roentgenogram, reproduced in Figure 4. As inspection shows, there was no area of the entire calvarium which was not affected by a multitude of tumors, many of which do not show in the roentgenogram because of the normal curvature of the calvarium. A similar condition existed in the sternum (Fig. 5) and also in all the ribs, which were affected throughout their entire length. With the exception of the first and second ribs, the entire shafts were practically destroyed, nothing but a very thin plate of decalcified bone of the thickness of paper remaining. Several score of healed fractures, some of them accompanied by considerable displacement, were present in the ribs,

and the heads of many of them were ankylosed to the vertebrae, which were practically unaffected, with the exception of the first thoracic and the second and fourth lumbar, which were slightly affected. The marked bone absorption accompanying the general tumor formation was responsible for the decided weakness of the ribs noticed during the inspection of the intact cadaver. The condition of the ribs was in marked contrast to that found in the former case in which all the large tumors in the ribs were definitely circumscribed and had

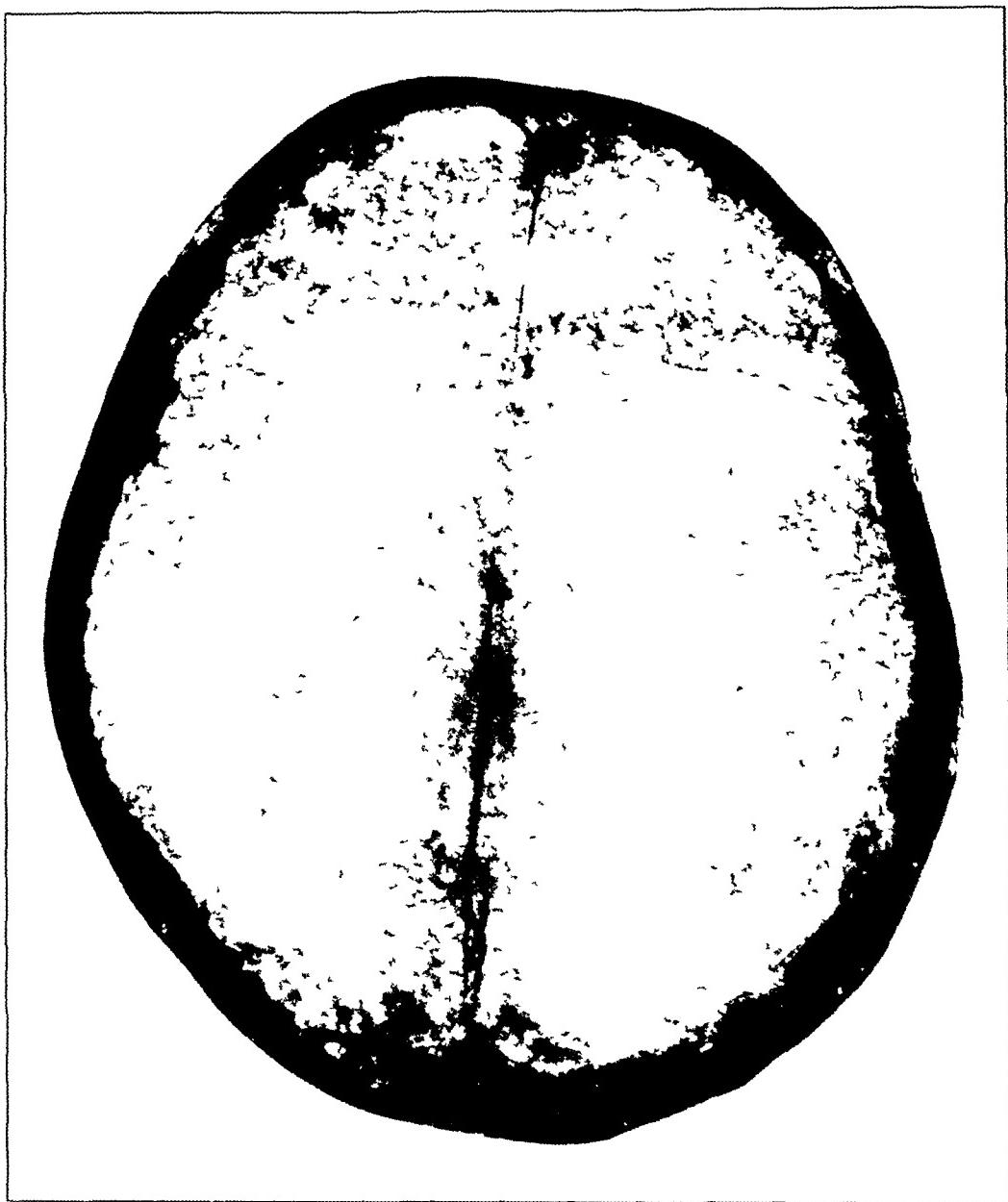


Fig 4.—Calvarium showing innumerable tumors

completely severed the affected bones. Moreover, in this case there was practically no decalcification beyond the immediate area of absorption.

The chief characteristic of the myelomatous condition in this second cadaver was the general dissemination of tumors throughout the ribs, sternum, skull and mandible. The rami of the latter and the greater portion of the corpora were completely affected with tumors, only a thin shell of compacta remaining in the region of the rami and angles, as shown in Figure 6. A roentgenogram

of the base of the skull (Figure 7) showed that it was affected as seriously as the calvarium, not even the zygomata or condyles being free of tumors.

Roentgenograms of the left upper extremity show that all of the scapula except the central portion of the body was almost as completely filled with tumors as the calvarium. The absence of tumors in the midportion of the scapula probably was due to the thinness of the spongiosa. The head and the tuberosities and the proximal portion of the surgical neck of the left humerus were practically unaffected, and little evidence of tumor formation was present in the condyles and epicondyles. The rest of the diaphysis showed the presence of



Fig. 5.—Sternum, showing innumerable tumors

large numbers of tumors. They lay in contact with each other throughout the entire extent of the medulla.

The left clavicle contained a callus, evidently due to fracture, about 35 cm from its distal extremity, and numerous tumors throughout its shaft. Only a thin shell of compacta remained in the greater portion of the distal two thirds of the bone.

The radius and ulna, particularly the latter, contained only slight evidences of the presence of tumors, except for the fact that the distal extremity of the ulna in the region of the styloid process seemed to have been affected. The

carpal bones of the right hand were practically normal, but the first, second, fourth and fifth metacarpals contained evidences of tumor formation. The phalanges of the thumb were free, but the middle and terminal phalanges of the second and third fingers were markedly affected and ankylosed.

The left ilium and ischium were much affected, though containing no single large tumor area such as that in the right ilium. The left femur was but slightly affected in its upper half with the exception of the head and tuberosity. The patella was clear, and the same thing seemed to be true of the tibia, but the diaphysis of the fibula apparently was affected slightly throughout its entire extent.

With the exception of the internal cuneiform, the bones of the left foot, the first metatarsal and the phalanges seemed to be unaffected, but the entire

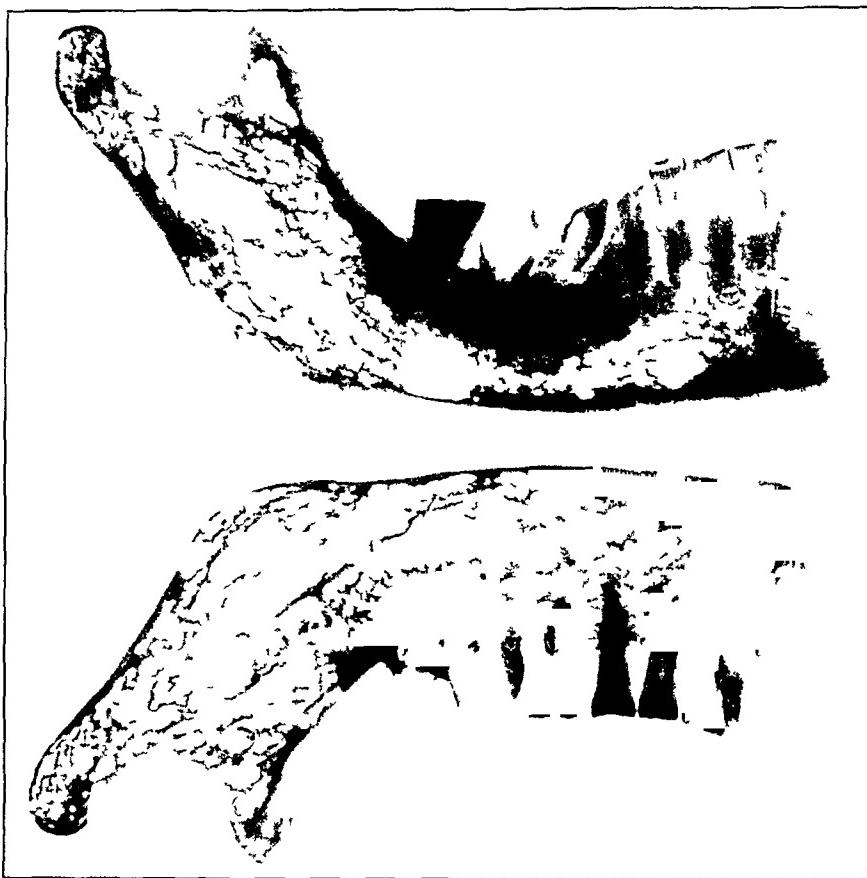


Fig. 6.—Mandible showing innumerable tumors, except in the mental region

right ilium, with the exception of the thin area in the middle, was extensively involved. A large oval area about 7 by 6 cm in size in the vicinity of the anterior superior spine formed one large tumor which was elevated slightly and irregularly above the normal surface though still covered by rough bone. A greater portion of the tuberosities of the ischium seemed unaffected.

The head, neck and tuberosities of the right femur and also the distal fifth of its diaphysis seemed to be wholly unaffected, but the rest of the diaphysis contained disseminated tumors. The lower half of the condyles of the tibia contained no recognizable tumors, and the rest of the bone contained only scattered ones. The entire diaphysis of the right fibula was greatly rarefied and contained scattered indications of circumscribed tumors. The roentgenograms suggest that the marrow of the entire bone was affected and that bone absorption was quite general. All the toes and the heads of the first

and fourth metatarsals contained evidences of tumors, but the rest of the right foot, with the exception of the lateral margin of the cuboid, seemed to be unaffected.

The condition of the right scapula was similar to that of the left, except that the inferior extremity had been fractured over an area of about 2 cm. This fragment, although displaced laterally about 4 mm, had completely united with the body. Callus formation was but slight, and only a small area of the



Fig 7—Base of the skull indicating extensive bone absorption also in this region.

central portion of the body was free from tumors, as judged by the roentgenogram. The superior, medial and lateral regions were entirely interspersed with tumors, the largest of which measured about 6 mm. Most of the spine and head, and the acromion and coracoid processes seemed free of tumors.

Aside from the marked deformity due to displacement and thickening of the proximal extremity of the right clavicle, the most noticeable thing in the roentgenogram of this bone was the extensive destruction of the shaft.

The condition of the right humerus was quite comparable to that of the left, the head and anatomic neck and the condyles and epicondyles containing no tumors.

The radius seemed only slightly affected in the greater portion of the diaphysis. The largest tumor, which measured only about 4 mm in diameter, was located distally to the radial tuberosity. The conditions of the diaphyses of the right ulna and fibula were similar to those existing on the left side.

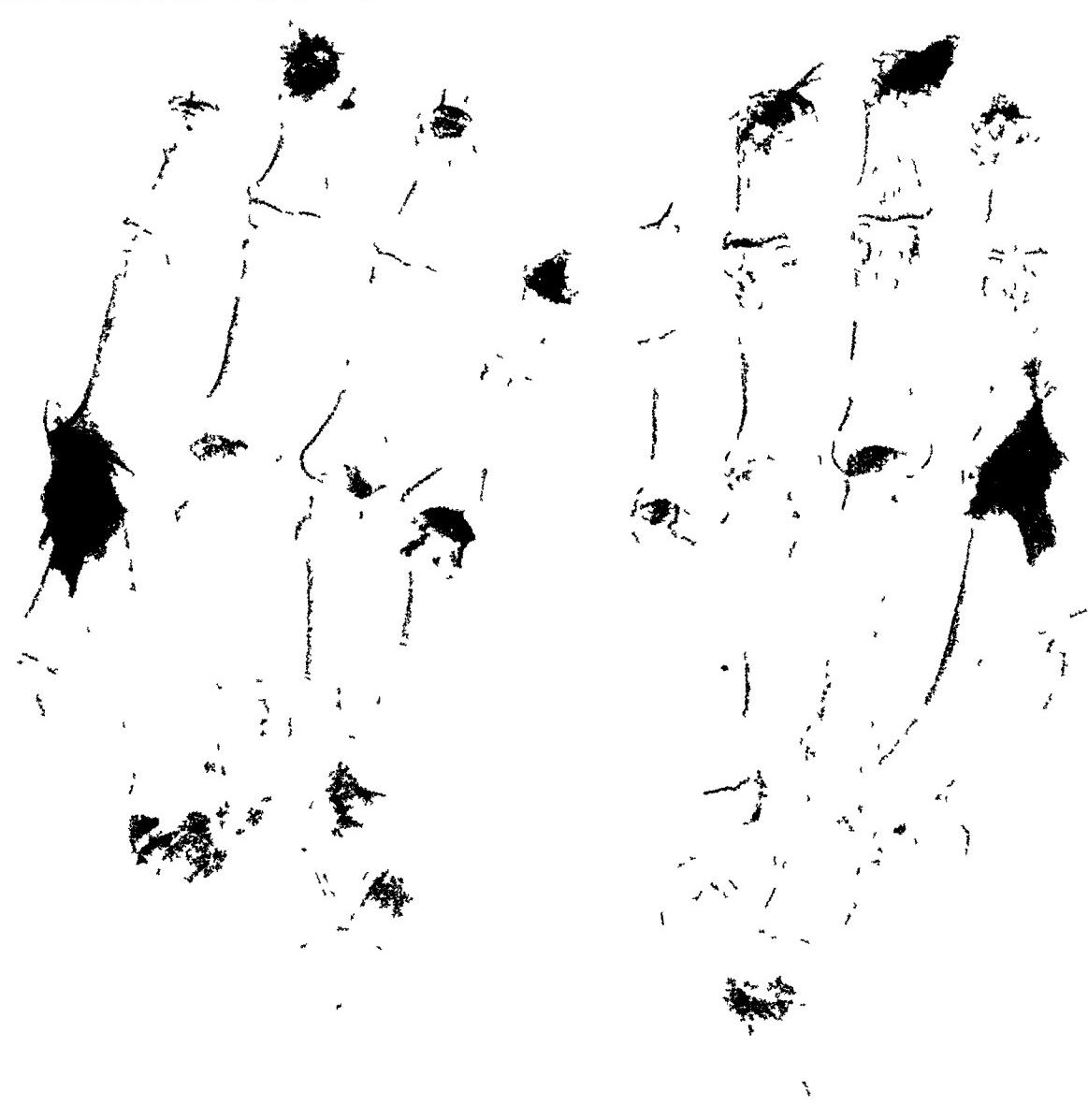


Fig. 8—*A*, left hand and wrist, showing the peculiar exostoses at the radio-ulnar articulation; *B*, right hand, showing identical conditions.

The fact that the osseous deformities on the distal extremities of the radius and ulna in the left arm were repeated almost exactly in the right is of particular interest. This duplication was practically identical even to the presence of the tumors in the styloid process of the ulna.

The condition of the metacarpals and phalanges was similar to that noted in the left hand.

A marked right scoliosis was present in the region of the second to sixth dorsal vertebrae. This was uncompensated for in the lumbar region, and careful examination of the entire spine failed to reveal any cause for it. However, since two old fractures were present in the right clavicle, it is not improbable that this scoliosis was the result of the posture assumed by the patient in an attempt to protect the more severely injured side.

Two small defects were present in the capsule of the left shoulder joint. Both were slitlike, the larger measuring about 1 cm in length and 3.5 mm in breadth, and both being located along the dorsal border of the tendon of the supraspinatus. The subcromial portion of the coraco-acromial ligament was worn, as was the entire outer surface of the upper portion of the articular capsule. The subdeltoid bursa was entirely intact, however, and not especially enlarged. The dorsal margin of the intra-capsular portion of the tendon of the long head of the biceps was frayed, but the articular cartilages of the shoulder joint were quite normal.

The capsule of the right shoulder joint was roughened and frayed, and the lateral border of the coraco-acromial ligament was worn to a sharp edge and somewhat frayed. This is particularly interesting since this ligament in the other arm still was continuous with the fibrous expansion which extended to its lateral margin from the coraco-brachialis and long head of the biceps.

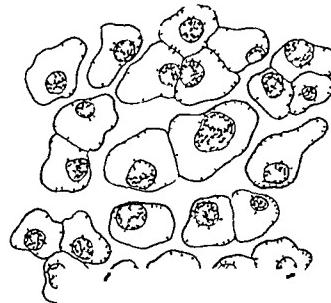


Fig 9.—A group of typical tumor cells

The tendon of the long head of the latter showed some calcification, and this is also true of the synovial villi in the interior of the joint. Calcium deposits were present also in the anterior portion of the capsule of the right elbow joint, in which the capitellum and the head of the radius had undergone changes similar to those present in the left arm. In brief, the conditions in the wrist and hand of this arm were similar to those in the left, even to the destruction of and deposit in the tendon of the extensor carpi ulnaris.

Numerous small calcific nodules were present, especially in the lateral portion of the capsule at the elbow joint, and almost the entire capitellum and the head of the radius were polished. Slight lipping was present throughout this joint, and the styloid process and head of the ulna, together with the corresponding articular surfaces on the distal extremity of the radius, were greatly deformed. The fibrocartilage on the ulna was completely destroyed and the medial portion of its distal extremity was formed by an osseous articular surface in the form of a trochlea, with a deep groove which received a markedly prominent and roughened bony ridge on the right radius, shown in Figure 8B. An almost identical condition in the left hand is shown in Figure 8A.

The articular cartilage of many of the carpals, metacarpals and phalanges were slightly or extensively eroded, and the middle and distal phalanges of the third finger almost firmly ankylosed. But the most interesting thing in this entire upper extremity was the presence of deposits in many of the articular cartilages. In the left hand, as in the right, these deposits were present not

only in all ankylosed articulations, but also in most others. Hence, it is not surprising that there was considerable erosion of the articular cartilages with but slight para-articular bony reaction. It is rather difficult to account for the marked distortion of the fingers, except for that in the terminal phalanges, on the basis of bony change.

Similar deposits in the cartilages accompanied by roughening and polishing were present in many articulations of the feet although the tibiotarsal articulations were quite normal. The deposit was most pronounced in the articular cartilages on the medial portions of the feet, that is in the regions of greatest strain. Strangely enough, no urates were found in the cartilages examined (Cajori).

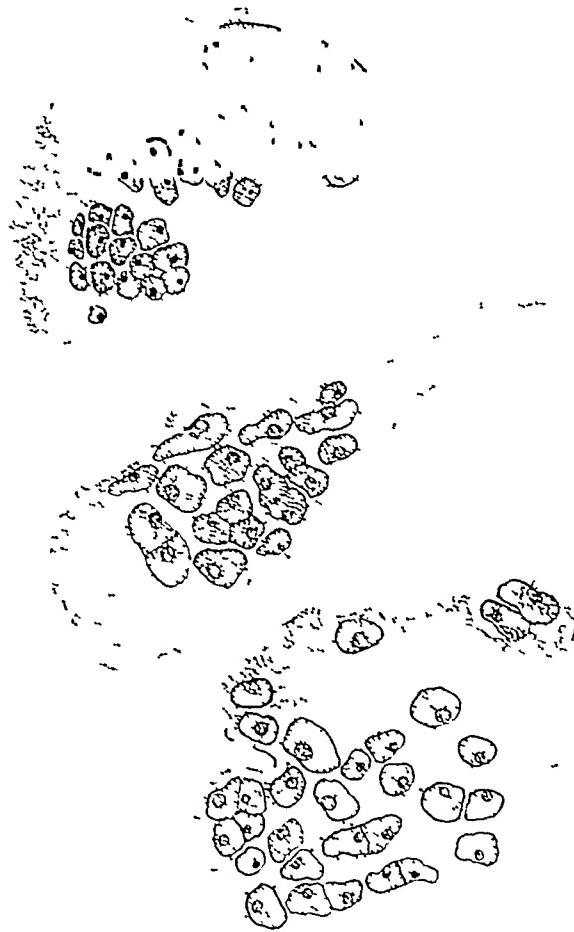


Fig 10.—A group of osteoclasts.

The deposits were not limited to the joint capsules, to the articular surfaces of some of the bones or to the subcutaneous tissues. They were found also in some of the deep flexor and the common extensor tendons of the fingers. However, they did not unite these tendons to the underlying bone, although some of the tendons were considerably thickened in the region of the deposits. That trauma probably was a factor determining the location of these tendon deposits is suggested, not only by their location in this case, but also by the fact that the worn tendon of the extensor carpi ulnaris, which was partly destroyed by friction through movement on the roughened, large exostosis in the region of the styloid process of the ulna, also contained deposits. Although slight evidences of wear were present in the right hip joint, similar deposits were absent here and also in the right knee joint, except that some of the synovial villi in this joint contained them.

The deposits in the superficial fascia were located in regions exposed to trauma. Except for those located on the fingers and in the tendons, they were small, some being barely visible to the unaided eye. It was particularly interesting that small deposits were found in the subcutaneous and subfascial bursae in the olecranal and in the prepatellar regions. Since it is but rarely that superimposed subcutaneous bursae are found in the olecranal region, it is more than likely that these elbows were subjected to more than ordinary friction. Both subcutaneous or superficial bursae of the olecranon were larger than usual, this being particularly true of the left one. Both subfascial or deep bursae were small, measuring only about 7 mm across, but the walls of both, as well as those of the subcutaneous bursae, did not suggest the existence of a former infection. I do not know whether slight trauma or friction may have been a factor in determining the location of these subcutaneous deposits, but their location necessarily suggests this. Only a few very small superficial deposits were noticed in the region of the feet, but these also were found in areas exposed to injury.

There was an entire absence of metastases in this, as in the previous case. The local calcium deposits also were in marked contrast both in location and in extent to those in the previous case. There was nothing in the viscera to attract special attention. The lungs, except for minute deposits which gave the cut surface a granular feeling, seemed quite normal. The spleen was decidedly below normal in weight. The aorta and all the great central vessels were in good condition, but the radial arteries were extremely sclerotic and calcified. The same was true of the vertebrals and the internal carotids in the more distal regions. The coronary arteries also were somewhat sclerotic as were the bicuspid and tricuspid valves. Nevertheless, these areas of sclerosis, as well as those in the arteries, would not have attracted attention by themselves. Although pronounced, they were not more so than those often found after death from causes unassociated with myelomata, nor were they so extensive.

Microscopic sections of portions of the tumors removed from the temporal region, the ribs and the ilium showed an entire absence of encapsulation. In many of the areas surrounding these tumors, there was so little connective tissue that one had to look carefully for it. This finding agrees with the fact that it was impossible to remove any of these tumors in their entirety as in the previous case. Indeed, considerable areas of these tumors seemed wholly free from stroma of any kind, the prevailing type of cell suggesting premyelocytes. Not uncommonly, these cells were arranged in cords about a vein, thus roughly simulating a liver lobule.

Although the preservation of these tumors was not adequate to permit a careful cytologic examination, it, nevertheless, was sufficiently good to reveal clearly the fact that there was uniformity in the size and character of the tumor cells. Most of these were from 10 to 12 microns in diameter, with a slightly granular cytoplasm and an eccentrically placed vesicular nucleus, as shown in Figure 9. In many of these nuclei a nucleolus was evident, but in others the chromatin was formed into small granules.

As reported also by other investigators, small, less well-preserved areas were scattered throughout the sections of these tumors. A careful search was made for different types of cells, but none were encountered, except that osteoclasts were present at the periphery of the tumors from the ribs and sternum and were also contained in sections from the large tumor-area in the right ilium. They were quite usual in type, as shown in Figure 10, and were found only at the periphery of the tumors from the ribs because the midportions of these tumors contained no osseous remnants.

The Haversian canals in the surrounding bone were in a condition quite similar to that found in the case previously reported except that there was an absence of an internal bounding layer of cells osteoblastic in character. No matter how wide these canals were, or how great or how irregular the bony

destruction, none (of those examined) contained osteoclasts. The latter were confined largely to the periphery of bony trabeculae and to spicules of bone which lay isolated in the cellular masses of the tumor.

No periosteal reaction was present where the tumors had perforated the bone in the temporal region. Yet the body contained scores of fractures which had healed without a great deal of displacement or an excessive formation of callus. Slight deposits of a brownish pigment were noticed, particularly in the affected regions from the temporal bone, small areas of which did not seem to show the presence of tumor cells. They contained shadow forms of fat cells instead. In other areas, the adipose marrow contained scattered tumor cells throughout its entire extent. This seems particularly interesting in view of the fact that the extremities of the long bones, where red marrow is retained longer, were not at all, or but very slightly, affected. The diaphyses of these bones, on the other hand, were markedly affected, in spite of the fact that the body was that of an individual 63 years of age. Hence, one either must assume that the myelomatous condition had existed for decades or that it encountered no difficulty in extending into or in beginning in fatty marrow. It is true, nevertheless, that the red marrow was affected more generally than the yellow. This is well exemplified by the condition of the calvarium, and by that of the entire skull, the ribs, the sternum and such long bones as the phalanges, the metacarpals and metatarsals and such short bones as the carpal and tarsals.

Microscopic examination of the large deposit over the distal interphalangeal articulation of the middle finger of the left hand revealed large areas many of which were composed exclusively of deposit. Some of these contained considerable quantities of yellowish pigment which, strangely enough, gave the impression of being diffuse in some areas. These deposits were transversed by many coarse trabeculae of fibrous connective tissue, some portions of which were decidedly infiltrated with large lymphocytes, most of which contained a somewhat more extended margin of cytoplasm. Not infrequently these areas of infiltration were located near blood vessels. Although the section examined contains a portion of the common extensor tendon, the latter did not contain deposit throughout its entire extent. A small portion of it contained a large mass near one side of which smaller deposits were found. A small portion of bone, apparently a portion of an exostosis, also showed the presence of some osteoclasts and considerable destruction. Aside from being very vascular, the subcutaneous tissues over this area showed nothing peculiar.

There was an entire absence in this skeleton, of anything that could be referred to as an exostoses except on the distal extremities of the radii and ulnae as shown in the roentgenograms of the hands.

Both coxal bones were decidedly massive with markedly roughened surfaces, especially over the ilium, due probably to reactions evoked in the periosteum. This seems the most likely explanation for the presence of the roughening since it was most marked in the regions where the tumors came nearest to the surface in these bones. It is interesting that no such roughening was present on any of the ribs, in the sternum or on the skull. Yet over the entire external surface of these bones, there were numerous small areas in which the tumors came very near to penetrating the compacta.

The roughening of the surfaces of these bones was indeed very similar to that present in the right tibia, the periosteum of which was somewhat adherent. The vessels were tortuous. Whether or not the marked anterior curvature of this tibia really was congenital, as suggested in the protocol, is open to doubt. The entire appearance of the surface of the bone suggests that it was syphilitic, although the curvature was not such as is regarded as typical in this disease. The extreme vascularity of the bone as judged by the many large vessels that perforate the diaphysis on all sides is as curious as the site of considerable ossification at the place of insertion of the popliteus.

CALCIUM AND PHOSPHORUS CONTENT OF THE TISSUES

Unusual conditions of mineral metabolism undoubtedly prevail during multiple myeloma. They are a result of the extensive lesions in osseous tissue characterized by the replacement of bone by tumor masses.

The attention of investigators has been attracted by the way in which the body disposes of the large amounts of calcium liberated from the bones. That a large part of it is excreted by way of the kidneys and intestines is clearly indicated by the observations of Williams¹² (1910-1911) and Blatherwick¹³ (1916). So great was the loss of calcium in the case studied by the latter, that the daily administration of 15 gm of calcium oxid was insufficient to secure a positive calcium balance.

Analysis of various tissues from cases of multiple myeloma indicates that frequently there is an infiltration of calcium salts in some parts of

Calcium and Phosphoric Acid Content of Tissues

Source of Specimen	Ash, %	CaO, %	P ₂ O ₅ , %	CaO % of Ash	P ₂ O ₅ , % of Ash	Ca, % of Ash	PO ₄ , %	10 Ca 6 PO ₄ (400 570)
Ribs	31.46	15.84	12.65	50.35	40.17	35.98	53.71	400.597
Skull	59.77	32.18	24.93	53.85	41.71	38.48	55.76	400.550
Femur	57.01	30.96	22.98	54.25	40.27	38.77	53.84	400.555
Femur	54.62	29.52	22.19	54.06	40.63	38.63	54.32	400.563
Rib tumors	5.78	1.51	2.59	26.02	44.87			
Finger deposits	15.41	2.77	1.40	18.00	9.09			
Trachea	6.21	1.06	0.47	17.10	7.68			
Stripped muscle	3.79	0.40	0.76	10.62	20.09			
Liver	4.56	0.49	0.74	10.89	16.39			
Lungs	5.00	0.26	0.96	5.18	19.28			
Spleen	5.91	0.37	3.30	6.27	5.09			

the body. Bender¹⁴ (1902) reports finding calcium deposits in the lungs, liver and lymph glands and in connective tissue. Tschistovitsch and Kolessnikoff¹⁵ (1909) analyzed several tissues from a case of myeloma and found an abnormally high ash content of the lungs, liver and kidney. In the case reported by Meyer and Swain (1918), the latter found that the percentage of calcium in the large deposits in the parietal pleura was 35.13. There also were excessive amounts of cal-

12 Williams, O. T., and Evans, E. R. A Case of Multiple Myeloma with Some Observations on the Nature of the "Bence-Jones" Protein Found in the Urine, with a Pathological Report on This and Another Case by E. Glynn, Lancet 2, 1910

13 Blatherwick, N. R. Calcium and Bence-Jones Protein Excretion in Multiple Myeloma, Am J M Sc 151 432 (March) 1916

14 Bender Ueber ein periostales Rundzellensarcom in ein Myelom mit Kalkmetastasen, Deutsch Ztschr f Chir 63 370, 1902

15 Tschistovitsch, T., and Kolessnikoff, Helene. Multiples diffuses Myelom (Myelomatosis ossium) mit reichlichen Kalkmetastasen in die Lungen und andere Organe. Virchow's Arch f path anat 197 112-135, 1909

cium in the muscles examined but a very low content in the bones. This was especially true of the bones in which there were extensive tumor lesions.

I analyzed a number of specimens of bones and other tissues from the case of multiple myeloma described in the present paper (Meyer). The samples of the ribs and skull were filled with innumerable tumors. For the sake of comparison, we took a section of the distal third of the diaphysis of the femur, that, judging from roentgen-ray examination, seemed to be free from tumors.

Several of the deposits over the distal interphalangeal joints described above were dissected out and analyzed. It also seemed desirable to study the actual tumor masses sufficient quantities of which were removed from the ribs. In addition samples of the liver, lungs, spleen, trachea and the quadriceps extensor muscle were examined.

Each specimen was prepared for analysis by dissecting it as completely as possible from adhering tissue. It was then cut into fine pieces and dried at 110°C to constant weight. The ashing was done in platinum dishes at a dull redness. The ash was dissolved in hydrochloric acid. Calcium was determined by the McCrudden method and phosphoric acid by the usual gravimetric procedure.

The analytic results are given in the accompanying table.

The ribs showed an extremely low ash content as compared with that of the apparently normal femur. Hence, it seems that actual decalcification of the bone, as suggested by gross examination, had taken place. It is rather surprising that a like result was not obtained in the calvarium, where the tumors were very numerous. A portion about 5 cm in diameter taken from the left parietal region was almost normal in composition.

It will be noted that the ratio of Ca to PO₄ in the bone samples is not far from 400 to 570, the ratio existing in normal bone. Swain (Meyer and Swain, 1918) also found that this ratio had not changed significantly in the myelomatous bones examined by him.

The low ash content of the tumor masses shows how completely the bone was decalcified in some regions. The low mineral content of the finger deposits dispelled the idea that these were composed mainly of lime salts. A few milligrams of the deposit were sufficient to give strongly positive murexid and phosphotungstic acid tests for uric acid. Hence the deposits were largely made up of salts of uric acid instead of calcium as seemed likely. I found no evidence of extensive deposits of calcium salts in any of the tissues examined, although the ash content of the muscle and liver was somewhat higher than that given by

Albu and Neuberg¹⁶ (1906) The trachea also shows a high calcium content, but these excesses do not account for the large quantity of calcium liberated from the bones

In view of these findings and the published reports of balance experiments on multiple myeloma, it seems probable that the calcium liberated in the destruction of bone tissue is rapidly and in a large part excreted from the body and, in relatively small amounts only, is deposited in other parts of the body

16 Albu, A., and Neuberg, C. Physiologie und Pathologie des Mineralstoffwechsels, Berlin, J. Springer, 1906

THE HISTOGENESIS AND NATURE OF GAUCHER'S DISEASE *

THEODORE R WAUGH, M D

AND

D S MACINTOSH, M D

MONTREAL

Although one of the main pathologic lesions, the primary idiopathic splenomegaly of Gaucher has been the subject of considerable discussion. This has centered more particularly around the cytogenesis of the characteristic large round to oval or polygonal single or multi-nucleated cells, which comprise the bulk of the splenic tissue and account for the splenic enlargement. Since the original neoplastic conception of the nature of these cells was replaced by that of a hyperplasia, there have grown up two schools, one tracing their origin to the endothelial lining of the venous sinuses, the other to the reticular tissue of the pulp. The former view has been supported by Bovaird, Downes, Wilson, and others, the latter by Schlagenhauer, Risel, De Jong and Van Heukelom, etc. A few have expressed the opinion that these cells may arise from either source.

Mandelbaum,¹ in 1912, called attention to the fact that up until then no one had shown any transitional stages in the development of these cells, either from the endothelium of the venous sinuses or from the reticular cells of the splenic pulp. Such changes, however, he stated, could be demonstrated in the lymph nodes where the process was not so far advanced, and here a reticular origin was suggested. In later papers,² appearing in 1916 and 1919, he expanded this idea, and considered it evident that a similar development occurred in the spleen, and, since there was a free communication of the sinuses with the pulp, it seemed possible that most of the free Gaucher cells within the sinuses had come from the surrounding pulp and were derivatives of the reticulum. He stated, however, that in all cases which he had examined, the process in the spleen was too far advanced to permit of exact determination as in the lymph nodes, and that there was no positive evidence

* From the Pathological Institute of McGill University and the Royal Victoria Hospital

1 Mandelbaum, F S A Contribution to the Pathology of Primary Splenomegaly (Gaucher Type), with the Report of an Autopsy on a Male Child Four and One Half Years of Age, *J Exper Med* **16** 797, 1912

2 Mandelbaum, F S, and Downey, Hal Histopathology and Biology of Gaucher's Disease (Large-Cell Splenomegaly), *Folia hematol* **20** 139, Arch **3**, 1916 Mandelbaum, F S Two Cases of Gaucher's Disease in Adults A Study of the Histopathology, Biology and Chemical Findings, *Am J M Sc* **147** 366 (March) 1919

in the spleen that the endothelium of the sinuses did not take part in the formation of large cells, and that the possible origin from this source could not be denied

The extraordinary opportunity for throwing light on this problem that would be offered by the examination of a spleen in which the lesion was not far advanced has, therefore, been generally recognized for some time. Such an organ was recently removed at the Royal Victoria Hospital. Both clinical history and pathologic examination indicated that the process was comparatively early. Consequently, at the suggestion and under the supervision of Professor Oertel, we carried on detailed histologic studies of the tissue. The results have been very instructive and give us a much clearer conception of this unique condition than has previously existed.

REPORT OF CASE

History—S. C., a Hebrew girl, aged 5 years, has always been apparently a comparatively healthy child. Two years before, she had scarlet fever, and at that time her physician noted that the spleen was abnormally large. It did not decrease in size on recovery. About a year later, she was examined again, and it was found that the spleen had enlarged quite rapidly since her illness. Subsequent examination, a few days prior to admission, showed that progressive enlargement had occurred. At this time, the liver extended three finger breadths below the costal margin, there was a somewhat sallow color with malar flush, and a fluctuating pulse was present. The child had felt perfectly well, never complained, played with the other children and enjoyed a good appetite. The condition was considered surgical and the patient was admitted to the Royal Victoria Hospital, service of Dr. George E. Armstrong, April 11, 1922.

The family history was negative. The father and mother were well. There was a son older and a daughter younger than the patient, both apparently normal and healthy.

Examination—The patient was well developed and well nourished and apparently of stated age. The contour of the body was normal except for a somewhat pendulous abdomen, which was moderately tense. The skin was sallow, and there was no appreciable darkening of the skin of the face and hands. The mucous membranes appeared normal. There was no cyanosis, edema or ascites. The pupils were equal and reacted actively to light and in accommodation. There was no wedge-shaped thickening of the conjunctivae. The temperature was 98 F., pulse, 110, respiration, 20.

Examination of the lymphatic system revealed no pathologic enlargement of the glands. The respiratory system was negative. The pulse was somewhat irregular, rapid (110) and of good volume and fair tension. The heart showed slight enlargement to the left. There were no adventitious sounds. The blood picture showed leukopenia with relative lymphocytosis, but was otherwise normal. The abdomen was large, somewhat firm and pot-shaped. On palpation, there was no muscular rigidity, but a certain resistance. The liver extended 3 finger breadths below the costal margin. It was not tender, and the surface and edge were smooth. The spleen was easily palpated and extended well below the umbilicus on the left side, passing to the right of the midline at its lower pole. Here, a definite notch could be felt. There was no evidence of any other palpable mass in the abdominal cavity, or any localized area of tenderness. The nervous, locomotor-integumentary and genito-urinary systems were negative.

Operation.—Splenectomy was performed, April 13, by Dr Armstrong. The patient had an uneventful recovery, and was discharged, April 28, showing improvement in color, and a suggestion of diminution in size of the liver.

General Pathologic Anatomy and Histology.—The spleen showed a uniform enlargement and preserved the usual shape, except for numerous notches. It weighed 345 gm and measured 16 by 9 by 4.5 cm. It appeared solid, but not firm in the sense of a fibrosis. The capsule was thin and smooth, wrinkled on bending the organ, and stripped with ease. Scattered over the surface were numerous pin-point gelatinous darker spots. On section, the cut surface appeared pale brick red and pulpy, and dripped a little blood. The trabeculae were not prominent, and there was no evidence of fibrosis. Scattered throughout the cut surface were small round discrete, pin-head sized points, pale and gelatinous, which resembled amyloid malpighian corpuscles. The splenic vessels could not be made out.

Sections, cut very thin and stained by the routine hematoxylineosin method, were first examined for general information, such as histologic arrangement, etc. The capsule showed nothing abnormal, and there was no evidence of any thickening. The trabeculae were seen springing from the inner side of the capsule in the usual way and dividing the splenic tissue into compartments. Both capsule and trabeculae showed the usual structure, fibrous connective tissue interspersed with a variable amount of smooth muscle cells.

The striking feature, as seen under low magnification, was the almost complete replacement of the pulp by alveolar spaces of various size and shape which contained the typical large, clear cells characteristic of Gaucher's disease. Many of these alveoli were lined by a layer of the Gaucher cells and contained free cells within the lumen. Others contained comparatively few of these cells, but were filled with erythrocytes. While a great many, the majority perhaps, were completely filled by these large cells and appeared as solid masses or cords. Thus, also, neighboring alveoli coalesced and were distorted into varying shapes. Such alveoli, filled or partly filled in varying degrees with large pale-staining cells, dominated the picture and made up by far the greater part of the splenic substance. The small amount of normal splenic pulp which remained was compressed into narrow strands and small triangular masses between these closely packed distended alveoli.

The alveoli of Gaucher cells showed great differences in size and shape (compare examination of serial sections below). Furthermore, their arrangement was most striking. Peripherally, under the capsule, they were for the most part large and loosely approximated, with little interalveolar substance. As one passed inward, however, they became more irregular in size and shape, and interpolated between them was a gradually increasing amount of uninvolved pulp. Finally, one approached irregular larger and smaller districts in which the large alveolar arrangement was in a great measure lost, and the Gaucher cells lay in groups and clusters. These districts of less involved splenic substance varied in size from a merely microscopic area to quite large territories. They were irregularly scattered throughout the bulk of the organ but never approached the capsulated surface. They are not to be confused with the malpighian corpuscles or isolated lymphoid follicles. The former appeared to be reduced in number, their vessels intact but with a swollen and protruding endothelial lining. The arrangement of the alveoli about the corpuscles was likewise peculiar. Instead of the lymphoid mantle forming a sleeve for the artery, it was more often eccentric and one side of the artery was relatively or completely free of lymphoid cells. Here, however, were seen small clusters of Gaucher cells which assumed a more alveolar arrangement as one drew away from the vessel. Some arteries were completely devoid of enveloping lymphoid tissue and were surrounded on all sides by, at first very small, then gradually larger, groups of Gaucher cells, until finally large acini were encountered. No Gaucher cells were found deeply within the corpuscle, but at its periphery occasional single or small clusters of these cells could be seen. The isolated

lymphoid areas with large pale staining so-called germinal centers were numerous. Around them, the arrangement was variable. Often, large alveoli pressed directly against the periphery of the lymphoid tissue, while in other places there were smaller and larger clusters of the Gaucher cells.

The alveolar spaces were inclosed by sinus walls which were composed of a basement membrane of endothelium and a very thin stroma of fibrous tissue. But the condition of the walls varied greatly with the advance of the process. If we commenced with an alveolus in which there was no actual distension of the wall by accumulated cells, it was found that the wall was well lined by endothelial cells. These cells had a faintly acidophilic cytoplasm and nuclei which were elongated and flattened and possessed rounded ends (typically endothelial). They did not tend to bulge into the lumen. Some of these cells showed a considerable variation in structure and staining affinity. The nucleus might stain deeply and the chromatin was then uniformly distributed. In others, the nucleus appeared swollen with the chromatin arranged in vesicular manner. The fibrous stroma of the wall acted as a supporting framework and as an intercellular substance for the endothelial cells. It consisted of very fine fibrils interlaced in various directions. In other, generally larger, alveoli the endothelial cells appeared stretched, compressed, flattened and atrophic, the nuclei were elongated and thinned, and stained deeply. Compared with these were sinuses in which the lining endothelial cells appeared larger than usual. Their cytoplasm was acidophilic (hematoxylin-eosin), their nuclei were swollen, elongated, oval and vesicular, and their chromatin was clumpy and was clearly aggregated to the nuclear membrane. Still others were in places devoid of endothelium, and the denuded fibrous connective tissue cells which were stretched remained clear between the Gaucher cells and the interalveolar capillaries.

About some alveoli, the sinus wall formed a complete circle, while in others it was incomplete and straits of communication between neighboring alveoli were to be observed. This was particularly the case in the areas described above where the alveoli were smaller and more irregular.

The alveoli were made up for the most part of the typical Gaucher cells. Their number within a sinus varied greatly, from a comparatively few, to those filling the sinus completely. In some alveoli these cells appeared distinct from the endothelial cells of the sinus wall. In others, they were attached immediately to the wall and no normal endothelium was seen. In selected sections, where the process was not too far advanced, the Gaucher cells appeared continuous with endothelial cells of the sinus wall and were definitely attached to them without any line of demarcation. Other areas showed the cells attached to the wall by a pedicle, having a broad base and a thin fibrillar stalk. Some were single, while others were united by processes to other cells which projected into the lumen as irregular masses. Many of the Gaucher cells lay free in the sinuses, singly and in clumps. In many instances, they lined the sinus wall in a single layer, in others, there were several layers in varying degrees conforming to the shape of the sinus. Many were united in syncytial manner, with irregular spaces between them. Finally, there were completely filled sinuses which appeared as solid masses or cords. In many of these, the lining wall which separated the individual sinuses had disappeared, and thus larger cell aggregates were formed.

Blood was present in a considerable number of the sinuses, and more particularly in those which were large, and had a central lumen and a narrow margin of Gaucher cells. The erythrocytes were often closely adherent to these cells, and in those sinuses in which there was a syncytial arrangement, blood cells lay in the small spaces between the Gaucher cells.

Individually, the Gaucher cells varied greatly in size and shape (from 20 to 50 microns and even larger). The shape depended largely on whether the cell was free, in clumps or in large masses. The free cells appeared rounded or spherical, while if compressed in masses the shape became altered, usually

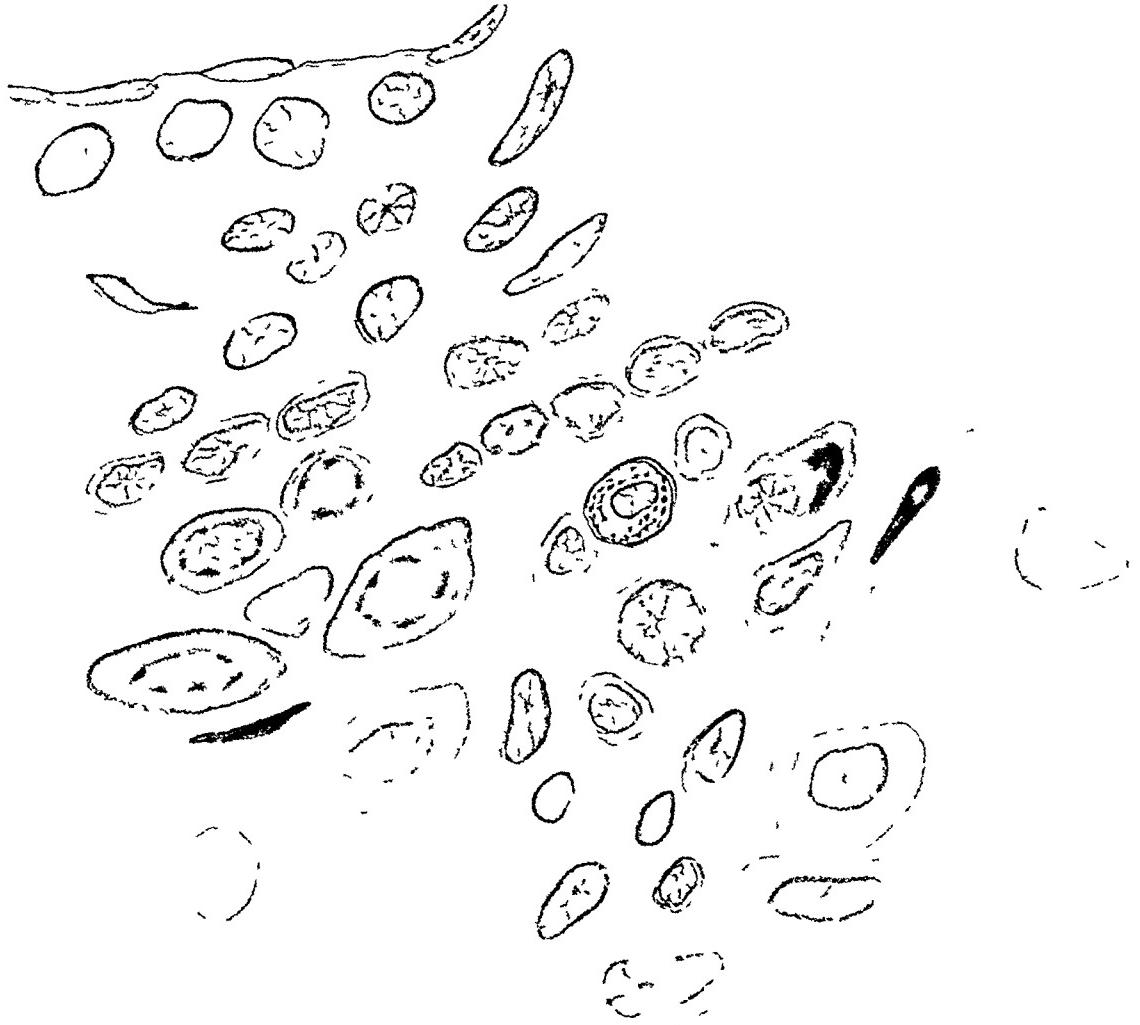


Fig 1—Camera lucida drawing of perivascular district, showing stages in differentiation of Gaucher cells

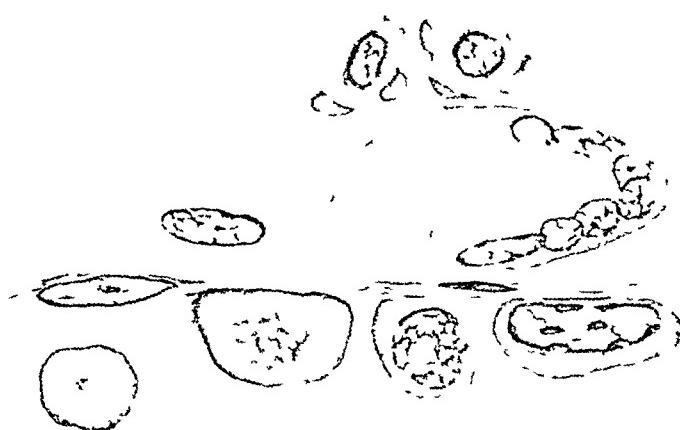


Fig 2—Camera lucida drawing, showing differentiation of endothelium lining a sinus

polyhedral. In other places, the outline of the cells could not be made out, but blended as a syncytium. Many had branching processes, which might be compared in appearance to the dendrites of nerve cells.

These cells stained with difficulty. Their cytoplasm was acidophilic, pale, swollen, turgid, vesicular and irregularly vacuolated. It had a fibrillated appearance, with very fine fibrils running in all directions, thus forming an irregular meshwork. Many cells appeared to be finely granular. The cytoplasm had a honeycombed appearance, a spongy network in which the paraplasmic fibers appeared to have taken up the stain and inclosed in their meshes a homogeneous unstained substance. In some cells, particularly in those near

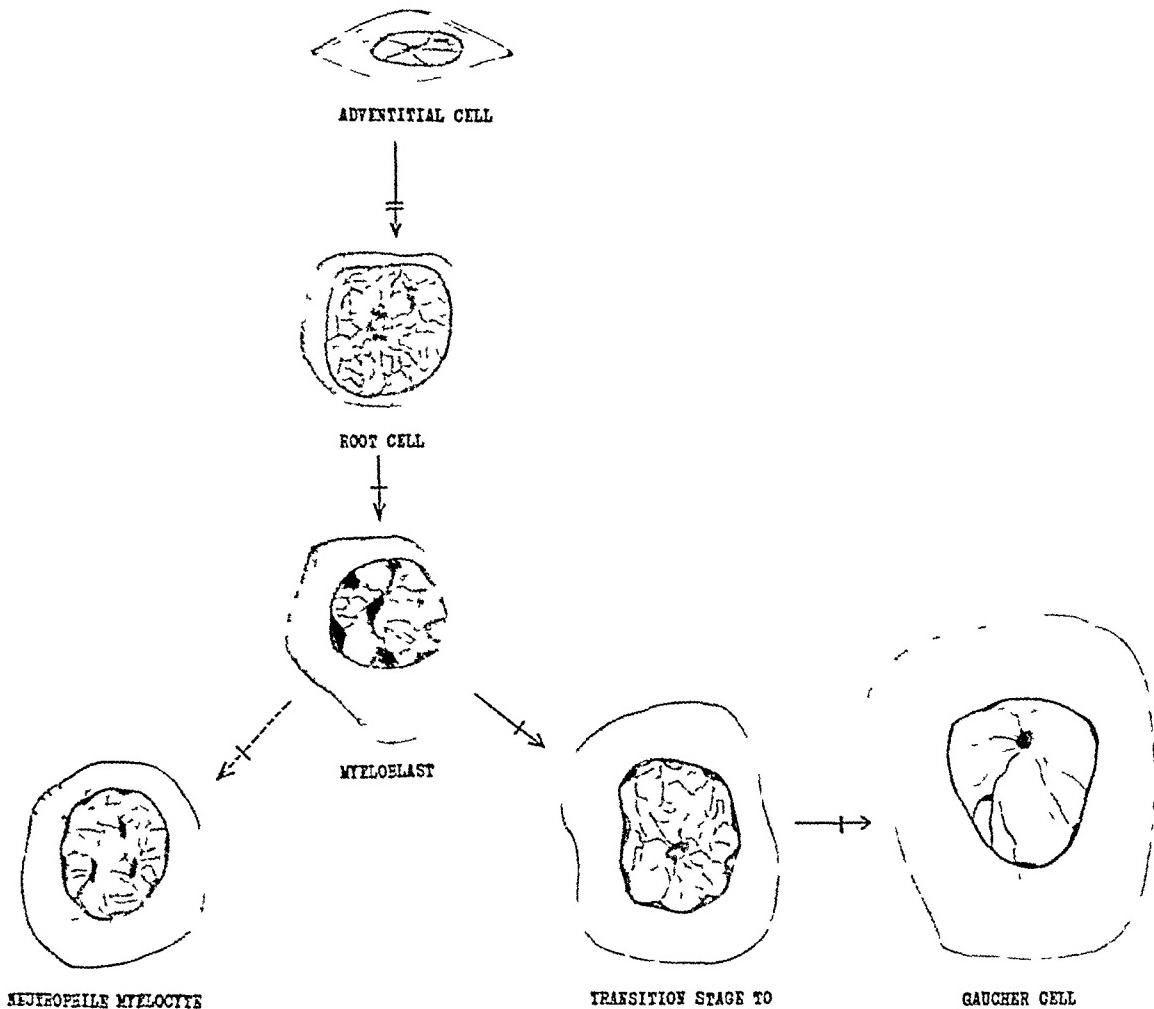


Fig. 3.—Diagrammatic scheme of cytogenesis of Gaucher cell

the endothelial lining of the sinus the cytoplasm stained much more deeply. It was acidophilic, with a purple tinge, appeared more homogeneous and more finely granular and exhibited smaller and less irregularly shaped vacuoles. Centrally, the cells were paler, more vacuolated and with indefinite irregular margins. Many of the cells were multinucleated, as many as seven nuclei being seen in a single cell. Frequently, there was only one. The nuclei were small as compared with the size of the cell and varied in position, many being eccentrically placed. They were usually round or oval, but were sometimes distorted, especially in the free cells. The nuclear membrane was prominent, and there was usually one or more nucleoli, or clumps of chromatin material. The majority of the nuclei appeared swollen, turgid and vesicular, with clumps and strands of chromatin material irregularly distributed over a very fine fibrillar

meshwork. In many, the chromatic material tended to be aggregated more densely around the periphery, thus giving the nucleus a darker rim with a paler center. In general, it may be said that the cells in small groups and those which lay at the periphery of large alveoli stained more deeply as regards both their cytoplasm and their nucleus, while the central cells of large alveoli were paler, swollen, washed-out in appearance and more often fused into multinucleated syncytia. Many of these larger cells contained in their cytoplasm a finely granular yellowish pigment.

Cytology and Cytogenesis of the Gaucher Cells.—Frozen sections were prepared from the spleen and the following special staining reactions carried out:

(a) For fats by the Sudan III and Nile blue reactions. No evidence for the presence of any fatty or lipoid substances could be seen in the Gaucher cells. Unstained sections were examined also with the polarizing microscope, but no anisotropic bodies were made out. This result is in contrast with the findings of Wahl and Richardson,³ who report anisotropic bodies in many of the large cells in their case, and positive staining reactions for lipoids.

(b) For amyloid with methyl-violet and acetic acid, and also with iodin and sulphuric acid. No trace of amyloid degeneration was found.

(c) For oxydase by the methods of Schultz and McJunkin-Charlton. The Gaucher cells were negative, while the neutrophilic and eosinophilic granular cells scattered throughout the tissue contained dark blue granules which caused them to stand out prominently.

Sections were examined in series particularly with the view of tracing the boundaries and relations of individual sinuses. It was found that, although they varied greatly in size, nevertheless many of the apparently small sinuses which contained but a few Gaucher cells were in reality but sections of large ones depending on the plane of cutting. Moreover, while the wall of a sinus might appear complete in one section, examined in series, it was found to have numerous apertures in which the endothelium and stroma were deficient and by which communications between sinuses themselves and sinuses and pulp were established.

Moreover, serial sections revealed the fact that, although many of the Gaucher cells appeared free in the sinuses, actually few if any were really unattached. In large dilated sinuses filled with blood and lined by a single layer of Gaucher cells which rested directly on the basement membrane and were often separated by endothelial cells, one could demonstrate that any apparently free cells were portions of finger-like projections extending into the lumen from the cells which lined the wall. These projections were often quite long, made up of several, often multinucleated cells, and swung as long tongues within the sinus.

In order to bring out in greater detail the acidophilic and basophilic staining qualities of the cells, tissue which had been fixed in Orth's solution was sectioned and stained by Pappenheim's method. By careful differentiation, the exact point at which these cell characteristics were most definitely shown was ascertained. These sections were cut especially thin and mounted in neutral balsam.

Stained by this method, the Gaucher cells were definitely oxyphilic. The nucleus was a pale blue, sometimes almost invisible in the mature cells, while the cytoplasm was a yellowish pink and contained a slightly deeper staining, also yellowish pink spongiplastic network. Interesting, however, is the fact that transitional stages up to this mature cell were seen. These were especially pronounced about blood vessels which were devoid of any lymphoid mantel. Here, one found in the adventitia groups of cells interpolated between its fibrous tissue. These lay in chains made up of two, three or even more cells and running longitudinally in the vessel wall. These cells were medium-sized,

³ Wahl, H. R., and Richardson, M. L. A Study of the Lipin Content of a Case of Gaucher's Disease in an Infant, Arch. Int. Med. 17: 238 (Feb.) 1916.

polygonal, often with flattened edges. Their cytoplasm was scanty, narrow and basophilic, their nucleus was relatively large and slightly irregular in outline to fit the shape of the cell, with reticular arrangement of the blue staining chromatin, which was aggregated into one, often more, nucleolus. These cells appeared to rise from other more definitely spindle-shaped, starlike cells which corresponded to the adventitial cells of Marchand. Cells showing transitional stages between the two were frequent.

Moreover, if one examined several of the cell strands described above, it was obvious that as one drew away into the perithelial tissue, the cell groups became larger until double rows of closely approximated cells appeared, and finally even irregular clusters. The majority of the cells of these groups remained at the same stage of differentiation, but one or two as a rule took on new qualities. They became larger as regards both cytoplasm and nucleus.

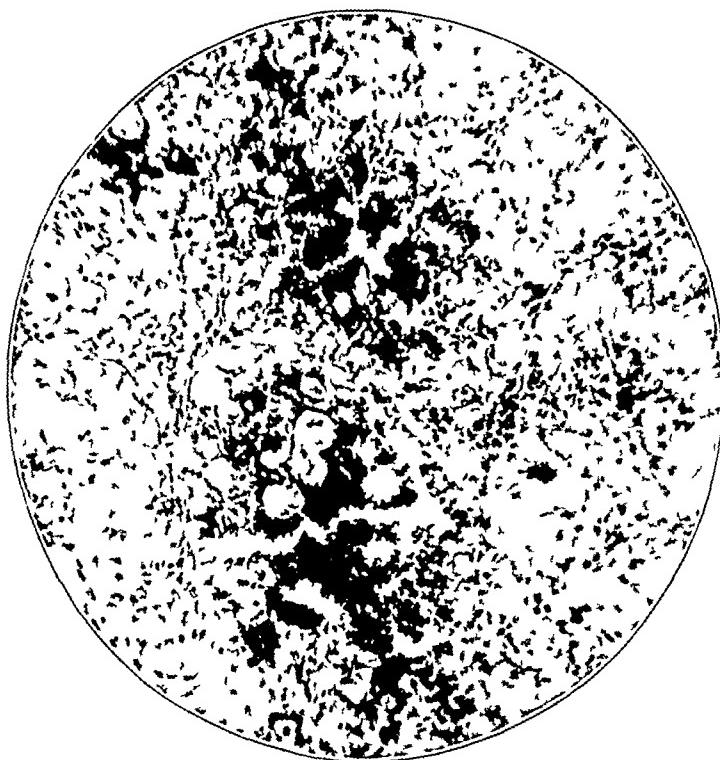


Fig 4.—Photomicrograph showing large dilated sinuses lined by Gaucher cells (Photo by M. Thomlinson)

The former was broad and nongranular, and stained predominantly blue, though there was a suggestion of pink mixed in, the latter was large, ovoid, vesicular, with a tendency for the chromatin to clump near the nuclear membrane. The cell at this stage strikingly resembled the embryonic myeloid cells (myeloblasts, leukoblasts) which are found in clusters in hyperplastic bone marrow.

In the irregular clusters of cells which lay between the strands and the more or less completely formed alveoli of typical Gaucher cells, the transition between the myeloid-like cell described above and the Gaucher cell was completed. At the same time, others of the more embryonic cells in the strand took on myeloid differentiation. Thus irregular clusters of myeloid cells appeared here, which contained an occasional cell, larger and possessing a broader and more oxyphilic cytoplasm. It had lost its preponderance of blue and now was pink with but a tinge of blue. Moreover, the nucleus had become much larger, less clearly defined and often lobated to a degree, though not exactly polymorphous. It still showed clumps of peripherally arranged chromatin. From

this point, it was but a step to the typical Gaucher cell, the cell broadened, appeared flatter and lost its basophilic qualities completely, that of the nucleus being the last to go.

Although the process has been described in graded steps, this gradual transition from the smaller basophilic undifferentiated cell to the large oxyphilic, highly differentiated cell of Gaucher occurs in reality through fluid stages. Mitotic figures are scarce, but occasionally occur in the smaller, less differentiated cells of the strands. Interesting is the fact that here and there among the irregular clusters of myeloid-like cells, cells with eosinophilic granules were present. These, as in the bone marrow, were of two varieties, one having a rather large vesicular paler-staining nucleus which tended to polymorphism, and the other having a smaller more diffusely staining nucleus which remained in the myelocyte stage. Furthermore, occasionally though much more rarely, mononuclear cells with neutrophilic granules were observed. Both of these granular cells, together with mast cells, were preserved even in the large alveoli, where they lay apparently more or less crowded between the large, fully differentiated Gaucher cells.

The characteristic transition described above, however, was not limited to the perithelial areas of the larger and smaller arterioles. It was also evident in the endothelium lining the venous sinuses. Small sinuses could be seen in the less involved areas which were lined by large endothelial cells, protruding more or less into the lumen and showing the same alterations in size and varying degrees of oxyphilia described above. Furthermore, in the large alveoli filled with Gaucher cells very often the lining endothelium remained, showing the same progressive transition. Actual transition of the pulp cells to Gaucher cells could not be made out. Small irregular clusters of Gaucher cells could be seen which appeared in no apparent definite relation, to either the vessels or the sinus walls, but the same transitional stages were not observed in these clusters.

COMMENT

In a discussion of the histogenesis and nature of this interesting condition, it hardly seems necessary here to go into the detail as to the various views brought forward by different authors. They have been reviewed recently by Barat.⁴ The original neoplastic conception has been quite generally discarded and recent study has concerned itself with the pros and cons of an endothelial or reticular origin of the characteristic cells. The facts associated with the argument are quite generally known as they have been gone over by numerous authors. The possible relation of the disease to the lipemias and cholesterol metabolism has been ably reviewed by Eppinger.⁵

There is one general outstanding feature of Gaucher's disease which appears to have been submerged somewhat in the detailed study of the cells themselves, and that is, that it is a disease of the hematopoietic system. Only those organs are involved which possess hematopoietic activity. They include primarily the bone marrow, spleen and lymph glands, and secondarily, other slumbering myelopotent areas in the liver, suprarenal, etc. They possess in common, and together constitute, the

⁴ Barat, Irene. Zur Histopathologie der grosszelligen Splenomegalie Typus Gaucher, *Folia hematol* **26**, Arch 3 (April) 1921.

⁵ Eppinger, H. Die Hepato-splenalen Erkrankungen, Berlin, Julius Springer, 1920.

great bulk of the reticulo-endothelial tissue of the body. The intimate relation of this tissue, or better, reticulo-endothelial system, to blood formation is now well recognized. It would appear, therefore, at the start, from the location of the lesion, that it is related to some type of hematopoietic activity. Moreover, its racial, familial and congenital nature suggests a condition which either exists deep within the organic constitution of the individual, or is concerned with the earlier development in still embryonic processes. Last, not least, the obvious origin and development of the specific Gaucher cells from endothelial and perithelial parent cells, as shown by this early case, is in agreement with this conception. Sabin and others have demonstrated an early embryonic origin of the blood cells from these, and only these, sources. Moreover, in extra-uterine life, as Grunei puts it, it is the slumbering peri-vascular adventitial cells that acquire, by an upset of equilibrium, either lymphoblastic or myeloblastic tendencies.

If these considerations of the general nature of the disease, its location and the origin of the cells point to a hematopoietic lesion, let us further examine the evidence by the cytogenetic changes in the cells themselves. The nature of the transition from the adventitial cells of the arterioles and the endothelial lining cells of the sinuses is at first essentially that of myeloid metaplasia. The large cells with basophilic cytoplasm and large ovoid vesicular nuclei, correspond to the primordial myelopotent blood cell (the myeloblast of Naegeli, the lymphoidocyte of Pappenheim). From these, owing to deposition of paraplasin in the interspongiplastic network, there occurs a gradually increasing oxyphilia which leads the cytoplasm of the cell by stages to the point of granule formation. Coincidentally, the nucleus displays typical clumping of the chromatin away from the parachromatin, in contrast to the less differentiated cell, where a fine network exists. Moreover, many of the nuclei exhibit a tendency to lobation, which is characteristic of developing myeloblasts. Unfortunately, in sectioned tissue that has been fixed and hardened, these changes cannot be observed with the precision characteristic of observations on blood smears, but the coarse changes are obvious and are strikingly similar to the myeloid changes observed in any hyperplastic leukogenetic bone marrow. The absence of oxydase in these developing cells might appear a strong argument against their myeloid nature, but it is a fact that such cells do not give the oxydase reaction in tissue sections under various circumstances, until they have attained a higher degree of differentiation. This was very manifest in sections from a case of subleukemic sarcoid myelosis which we recently examined. Here, large areas of myeloid metaplasia were quite free from oxydase, while others gave very strong positive reactions. Its presence under pathologic conditions is, therefore, variable.

Approaching now the stage of granule formation within the cytoplasm of the cells, there occurs a notable deviation from normal myelopoiesis. The vast majority of the cells at this stage undergo a peculiar type of swelling associated with a diffuse oxyphilic transformation, involving first the cytoplasm and ultimately the whole cell. Thus, they acquire the typical Gaucher cell characteristics. No true granules are formed, though the whole cytoplasm assumes a granular-like composition. The presence of eosinophilic granular myelocytes closely associated with the other cells suggests the possibility that, as regards this particular line, the progress of cell development is regular. Furthermore, occasional neutrophilic and basophilic granular mononuclear cells are observed.

As to the exact physicochemical nature of the oxyphilic change, little can be said. Neither the idea of protoplasmic hypertrophy nor of albuminous deposition adds a great deal to our conception, and we should be inclined to look on it as an excessive continuation or perversion of the usual matutative activities that result in the discharge of acidophilic, broken-down products into the cell body.

Such a conception of perverse myelopoiesis, or dysmyeloplasia, is not without support from previously reported cases of the disease. If, with this conception in mind, we review the descriptions of various authors of their cases, we are struck by the number of otherwise unexplained facts that fit in with it. For example, in the case recently (1921) reported by Foot and Ladd,⁶ attention is called to the acidophilic and hypertrophic condition of the adventitial cells of the smaller arteries. In the case described by Babes, Aurel and Babes (1913),⁷ there is an extraordinary tendency to eosinophilia, there being not only many eosinophile polymorphonuclei present, but eosinophilic granulation of the large cells themselves. Mandlebaum,¹ in 1912, called attention to the eosinophil and neutrophil myelocytes in the involved lymph nodes. In the case reported by Mandlebaum and Downey,² in 1916, it is stated that the Gaucher cells are "particularly numerous just beyond the wall of the larger veins or within their adventitial coat," where these writers consider that they arise from connective tissue.

Moreover, the conception is not without support from other somewhat allied conditions. In myeloid metaplasia of the spleen, as Naegeli⁸ and Pappenheim emphasize, the process takes origin from the perivascular connective tissue, more particularly from the slumbering clasmocytes, which under specific irritation proliferate and differentiate to form

6 Foot, N. C., and Ladd, W. E. Report of a Case of Gaucher's Splenomegaly, Am. J. Dis. Child. 21: 426 (May) 1921.

7 Babes, V., Aurel, and Babes, A. Un cas de maladie de Gaucher avec grandes cellules eosinophiles, Compt. rend. Soc. de Biol., No. 36, p. 575, 1913.

8 Naegeli, O. Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1923.

at first embryonic and then more mature myeloid cells. The lymphoid areas are not involved primarily but are brought to atrophy eventually by the pressure on their periphery of the myeloblastic cells. In the liver, the initial seat of the transformation is the region of the liver capillaries. The general similarity of the two processes is striking. Noteworthy, also, though possibly with slight significance, is the fact that tuberculosis is by far the most commonly associated disease in both the myeloid leukemias and primary splenomegalies.

The very slight morphologic changes in, and the relatively normal appearance of, the circulating blood in Gaucher's disease might at first be considered as a strong argument against the hematopoietic conception. However, one must bear in mind that, as in the usual myeloid metaplasias, not the whole hematopoietic system is involved at once but that the spleen, which is phylogenetically and ontogenetically the last of the blood-forming organs to give up its active blood-cell formation, is again the first to resume activity, and is followed later by the others. The bone marrow may continue for some time uninvolved. Furthermore we are as yet quite ignorant of the factors which determine whether a pathologic cytoplasia shall remain aleukemic or become leukemic. These factors, it would appear, act more or less independently of the primary pathologic process. Thus the sudden transition from aleukemic to leukemic conditions, as in lymphadenosis, is not attributable to any sudden change in the nature of the original lesions but rather to some alteration of controlling influences. Thus also a normal blood picture is present in many diseases of the hematopoietic organs as, for example, in multiple myeloma. Here, we deal with a systemic disease of the bone marrow itself, with normal and abnormal types of myeloid proliferation and still the blood picture remains unaffected. Hence, may we not have quite as readily in Gaucher's disease a normal and perverse myelopoiesis proceeding coincidently in separate organs without apparent alteration of the circulating blood?

Therefore from the histologic studies of this early case, coupled with a review of previously reported cases and a consideration of allied conditions we are inclined to the view that the splenomegaly of Gaucher is essentially a primary, probably congenital, progressive systemic disease of the hematopoietic tissues, characterized by an aleukemic dysmyelosis; that is, an irregular perverse myeloid metaplasia. The cells arise from the slumbering myelopotent cells of the reticulo-endothelial tissue of the hematopoietic organs. These are principally, and at first the adventitial cells of the blood channels and the endothelium of the sinuses. Possibly, later, the closely related reticulum also takes on a similar activity. As to its etiology, little can be said. Its true cause as that of other aleukemic and leukemic so-called blood diseases awaits an explanation in a

clearer understanding of the finer details of embryonic and postnatal hematopoiesis, which is quite beyond the bounds of our present knowledge. However, its racial, familial, sexual and congenital characteristics, and its connection with the hematopoietic system, indicative of a deep-seated plasmic alteration, make the conception of Naegeli that it is a constitutional anomaly, that is, a mutation in the human species, worthy of consideration.

EXPERIMENTAL CHRONIC GLOMERULONEPHRITIS *

LOUIS LEITER, M.D.

CHICAGO

In recent years, the problem of chronic nephritis has become, to some extent, restricted to the question of chronic glomerulonephritis. This type of kidney disease is almost undoubtedly of toxic or infectious origin, and, therefore, some measure of prophylactic treatment should be possible. With human material, obtained at necropsy, it is extremely difficult to trace the origin and development of this progressive nephritis, chiefly because, at different stages, the kidney presents various gross and microscopic appearances, seemingly distinct conditions, hence, the origin of the numerous classifications seen in clinical and pathologic descriptions. Were it possible to reproduce experimentally in one of the lower animals a condition in the kidneys simulating the chronic glomerulonephritis seen in man, a vast field of useful study would at once be opened, and great progress would be made in our knowledge of an extremely common and serious pathologic entity.

I REVIEW OF THE LITERATURE

A review of the literature on chronic glomerulonephritis presents at once a difficult and disconcerting problem. It is impossible to avoid frequent reference to the extensive work on the production of experimental acute nephritis, because in many instances the same measures employed to cause acute changes have been tried with a view to effecting more lasting, or chronic, injury. Furthermore, throughout the earlier literature there is found but rarely any attempt to distinguish between chronic glomerulonephritis and chronic nephritis, the latter term being used to denote anything in the way of degenerative or inflammatory conditions which present the appearance of a chronic process. It is obvious, then, that even a careful review of the literature will still leave considerable confusion in the mind of the reader. No attempt has been made here to include everything that has been written or done on the problem of experimental chronic glomerulonephritis. What has been hoped for in the distillation and condensation of the mass of written matter is an arrival at a simple, clear and honest criticism in the light of present knowledge, for the benefit of future workers in this field.

* This work was carried out in the John McCormick Institute for Infectious Diseases while the author was a Medical Fellow of the National Research Council in the Department of Pathology, University of Chicago, and Medical Resident at the Cook County Hospital, Chicago. The author is deeply grateful to Professor Ludwig Hektoen for extending all the privileges and facilities of the Institute.

The early studies on experimental acute nephritis brought out the interesting fact that some poisons injure the tubular epithelium severely, while others attack the glomerular capillary endothelium. Among the former poisons are uranium nitrate, potassium chromate and corrosive sublimate, while arsenic, cantharidin and snake venom belong to the latter group. Diphtheria toxin affects both glomeruli and tubules to nearly an equal extent. In the Harvey Lecture of 1910, Pearce¹ reviewed the early work, and pointed out that the different types of nephritis produced by means of these poisons were probably due to injury at different points of elimination. He insisted, however, that the distinction between so-called "tubular" and "vascular" poisons was not an absolute one, for already in 1907 Schlayer and his co-workers had shown, by physiologic methods, that the action of these poisons was more diffuse and less select than had been supposed. For example, in the late stages of uranium nephritis, a distinct disturbance in the vascular response was noted. Yet uranium was considered a good "tubular" poison. No one at present disputes the fact that one cannot injure the glomeruli seriously without simultaneously or subsequently damaging the tubules, and vice versa.

After these early experiences with acute nephritis, the above-mentioned poisons were used in the attempts to obtain a chronic nephritis. In 1904, Pearce tells us, Lyon tried cantharidin, corrosive sublimate and diphtheria toxin, known glomerular poisons. He found that the acute lesions disappeared rapidly and often recovery ensued. As Pearce states, if one includes in the term "chronic nephritis" a persistent kidney lesion characterized during life by elimination of albumin and casts, and histologically by changes involving glomeruli, tubules and connective tissue, nearly all experimental efforts can be excluded. It will be seen later how true this statement is.

Ophuls,² in 1907, reported on the effects of administration of lead salts by mouth in increasing doses over long periods of time. Guinea-pigs and dogs were used. Because of the anemia produced by the lead, it was difficult to keep the animals alive long. The guinea-pigs showed relatively unimportant renal changes. In dogs, marked chronic interstitial nephritis was found, yet there was no albuminuria nor cylindruria. Arteriosclerosis was not seen, and a true glomerulonephritis was not present.

Perhaps the poison most commonly employed in connection with experimental chronic nephritis was uranium nitrate. In 1909, Dickson³

1 Pearce, R M Problems of Experimental Nephritis, Arch Int Med **5** 133 (Feb.) 1910

2 Ophuls, W Experimental Chronic Nephritis, J A M A **48** 483 (Feb 9) 1907

3 Dickson, E C Experimental Production of Chronic Nephritis in Animals by the Use of Uranium Nitrate, Arch Int Med **3** 375 (June) 1909

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³ Dickson, E. C. Experimental Production of Chronic Nephritis in Animals by the Use of Uranium Nitrate, *Arch Int Med* **3** 375 (June) 1909

reported an extensive research with this substance. In eight guinea-pigs given from forty-six to eighty-seven doses of 0.25 mg uranium nitrate subcutaneously over a period of from seventy-seven to 120 days he found dilated glomerular tufts, with "cysts, some thickening of the capsule of Bowman and hyaline degeneration of the basement membrane. Round cell infiltration was noted but no fibrosis. In another series of seven animals which received 2.5 mg doses of the poison at intervals of from ten to thirty days for periods of from seventy to 111 days definite attacks of acute nephritis occurred followed by recovery of the animals. In these, the surface of the kidney was found dimpled new connective tissue had formed, and there was new elastic tissue around Bowman's capsule. A third series of fourteen animals received a single injection of 5 mg of uranium nitrate which resulted in a severe nephritis. While chronic changes were produced in some animals there was a marked tendency to recuperation. Dickson stated that these lesions (described above) closely resembled subacute and chronic diffuse nephritis in man. It would be going too far, however, to say that he was dealing with a true glomerulonephritis. The same criticism applies to his work in 1912.⁴

As regards the actual morphologic effect of uranium on the glomeruli we are indebted for our knowledge to Christian and his co-workers. In 1908 he pointed out the occurrence of peculiar hyaline droplets in the glomerular capillary endothelium of the rabbit kidney injured by uranium. This he considered a degenerative process. This peculiar lesion was limited to the specialized glomerular capillary. No other vessels in the body showed it. Later on in 1913, Christian and O'Hare summarized their extensive work on the actual anatomic changes in acute uranium nephritis in rabbits by stating that several types of glomerular lesions occur—hyaline droplets in the endothelium of the tuft fibrin thrombi in the capillaries, hemorrhages into the tuft with slow coagulation, dilatation of Bowman's space with a granular material and proliferation of the endothelium of the tuft and less often of the capsular epithelium. The findings have been confirmed repeatedly.

In 1911, Christian⁵ and his associates attacked the problem of producing chronic lesions in the glomeruli. Rabbits and guinea-pigs were given repeated doses of uranium nitrate or potassium bichromate for months. Round-cell infiltration was found quite constantly while connective tissue increase occurred in the form of triangular foci running

⁴ Dickson E C. Further Report on Production of Experimental Chronic Nephritis in Animals by the Administration of Uranium Nitrate, *Arch Int Med* 9: 557 (May) 1912.

⁵ Christian, H A and O'Hare J P. *J M Research* 28: 227, 1913.

⁶ Christian, H A, Smith, R. M., and Walker, I C. Experimental Cardio-renal Disease, *Arch Int Med* 8: 468 (Oct) 1911.

into the cortex from the periphery, the apex pointing inward. In these areas, the tubules were destroyed. The glomeruli were relatively little involved. This is an excellent description for the focal scars of "spontaneous" nephritis.

Further work with uranium was done by Baehr,⁷ who, in 1913, published the results of the injection of a single, minute dose of uranium nitrate—from 0.35 to 0.8 mg—subcutaneously in rabbits. His idea was to use just enough uranium to injure the glomeruli but insufficient to cause the usually extensive tubular degeneration. Of ten animals so treated, only one rabbit showed a definite glomerular lesion characterized by adhesion of the tuft to the capsule, epithelial crescents and albuminous exudate in Bowman's space. Apparently, this one animal was unusually sensitive to uranium. In eleven rabbits in which injection of from 0.35 to 0.8 mg of uranium nitrate was made directly into one renal artery, extensive glomerular lesions were produced, affecting, in some cases, 40 or 50 per cent of the glomeruli. Baehr described four stages in the affected glomeruli: coagulation necrosis of the capillaries, growth of the capsular epithelium to form a syncytium, secondary canalization of the glomerular mass by new capillaries and hyaline changes in the tuft with adhesions to the capsule.

In 1914, Wiesel and Hess,⁸ working on a similar principle of small dosage of poison, injected seventy rabbits with uranium nitrate intraperitoneally and epinephrin intravenously. They produced swelling, hemorrhage and exudation in the glomeruli, with, later, proliferation, organization and contraction. Eventually, they state, contracted kidneys resulted. No one has ever been able to reproduce these findings. Roth and Bloss⁹ repeated this work on sixteen rabbits, in 1922, but obtained only the usual tubular changes without significant glomerular changes except for hyaline droplets in the capillary endothelium in four animals.

Another substance which has been used to injure the glomeruli is snake venom. In 1909, Pearce¹⁰ injected twenty-one rabbits with from 1 to 2 mg of crotalus venom, in divided doses. All but one of the animals were killed within six days. The characteristic lesions were of two main types: hemorrhages into the tufts, but not into Bowman's space, and exudation of red cells, serum and fibrin, with or without hemorrhage. Hemorrhage into the tuft gave cystlike structures. Leukocytes were seldom seen. The tubular epithelium and the cells lining Bowman's capsule were not injured. The action of the venom

7 Baehr Ziegler's Beitr z Path Anat u z allg Path **55** 545, 1913

8 Wiesel and Hess Virchows Arch f path Anat, 1914

9 Roth and Bloss Virchows Arch f path Anat **238** 325, 1922

10 Pearce, R M J Exper Med **11** 532, 1909

was, therefore, selective on capillary endothelium, dissolving it, as had been previously shown by Flexner and Noguchi, in 1902.

Following up this work in 1913, Pearce¹¹ injected twenty-four rabbits repeatedly with the crotalus venom. No animal could be kept alive more than six or seven weeks. In the kidneys of these animals, there was noted proliferation of the endothelium of the tufts. The above mentioned hemorrhagic and exudative lesions were also present. Proliferation was not seen in the exudative type but was present in the hemorrhagic form. In other words, there was simply an organization of the thrombus. In those animals which lived the longest (from twenty-six to thirty-eight days), little glomerular change was found, although tubular degeneration was extensive. In dogs, the venom was much more fatal than in rabbits. Only tubular degeneration was produced, with hyaline changes in the glomerular capillaries. No evidence of reparative or subacute glomerular lesions was seen in dogs. Pearce concluded that the early lesions produced by crotalus venom did not tend to become chronic.

More successful results have been reported in 1921 by Suzuki¹². He used "Habu" venom (*Taimelesurus flavoridis*, Hall). This is said to produce marked glomerular injury, with little tubular damage. Rabbits were given from 3 to 4 mg per kilogram of body weight, intravenously. The susceptibility of the animals varied considerably as to the lethal dose and the effect on the kidneys. In animals dying within a few days, "cysts" appeared in the glomeruli, due, the author claims, not to rupture of the tuft but to extreme dilatation of one of the capillary loops. These "cysts" usually contained red cells, fibrin and a mass of what was probably platelets—apparently a thrombus. There was usually only one "cyst," occupying from one-third to one-half of the glomerulus ordinarily. Only one-quarter of the glomeruli were involved. In animals that lived more than a week, marked endothelial proliferation was noted. After from ten to fourteen days, degenerative changes appeared in the arterioles of the kidney, while the tubules underwent atrophy. After five or six weeks, an increase in the interstitial tissue was noted, particularly about Bowman's capsule. Fine granulation (or pitting?) of the surface of the kidney was seen. According to Suzuki, these "Schrumpfniere" are produced by the obstruction to the flow of blood through the glomerulus in the early stages, while the tubular atrophy and fibrosis are secondary phenomena. The capsular epithelium changes little. Epithelial crescents are not described by Suzuki. This nephritis does not tend to become progressive. Con-

11 Pearce, R M J Exper Med 18: 149, 1913.

12 Suzuki, T Mitt a d Path Inst d kais Univ z Sendai, Japan 1: 225, 243, 1919-1921.

siderable recovery occurs within a few months To speak of these kidneys as "Schrumpfniere," when they are not at all contracted, is somewhat far-fetched

Suzuki was, apparently, not satisfied with the chronic changes noted above and went on to attempt to produce a chronic glomerulonephritis He injected (A) eight rabbits with one or more large doses of "Habu" venom, and (B) more than twenty rabbits with one or more moderate doses In the B group, the left kidney was removed surgically some time after the first injection and studied as a control for the earlier changes in the kidneys The animals were allowed to live many months According to Suzuki, granular kidneys were produced, yet the gross description of these kidneys corresponds well with that which will be given later for the so-called "spontaneous" nephritis of rabbits Tubular changes are described in great histologic detail In fact, the author goes so far as to divide the kidney lesions into "chronic parenchymatous" and "chronic interstitial" types, the former type being the one with little glomerular change When one kidney was removed, the other showed much more atrophy and "contraction," which Suzuki blames on the effects of retained metabolic waste-products since the "Habu" poison could not act so long Yet the atrophic areas were always focal, not diffuse, and not progressive lesions In spite of the lengthy descriptions, discussions and speculations of Suzuki, one does not get the impression that he has produced a glomerulonephritis of the chronic variety Unfortunately, there are no illustrations in his articles

Diphtheria toxin has been frequently used in connection with experimental nephritis Bailey,¹³ in 1917, injected rabbits with diphtheria toxin alone, or in combination with pituitary extract In some animals, a high grade of degenerative arteriosclerosis was found, affecting, chiefly, the media in all the large vessels In the kidneys were found swelling and desquamation of the endothelial cells, fibrin thrombi and hyaline masses in necrotic capillaries of the tufts, with hemorrhages in some, and, in some glomeruli, collections of polymorphonuclear leukocytes Bailey believed that these changes resembled closely those found in acute and subacute glomerulonephritis in man But this interpretation is questionable There were no proliferative changes

In the same year, 1917, Faber¹⁴ carried out an extensive study on twenty-three rabbits, all of whom died or were killed within ten days He injected from 0.001 to 0.02 c.c. of diphtheria toxin (1 c.c. containing 200 minimum lethal doses) According to him, the primary change with a small dose, was endothelial proliferation in the tuft With larger doses, degenerative changes set in, until finally the glomerular capil-

13 Bailey, C. H. J. Exper. Med. 25: 109 (Jan.) 1917

14 Faber, H. K. J. Exper. Med. 26: 139 (Aug.) 1917

laries ruptured and globular hemorrhages into the tuft, the so-called "blood-cysts," occurred. The characteristic lesion of human hemorrhagic glomerulonephritis—fibrin, red blood cells and leukocytes in the capsular space—was notably absent. At most, the only exudate was albuminous. With still larger doses, thrombotic masses formed, probably necrotic cytoplasm of the endothelium. Leukocytes were scarce. Tubular changes were apparently secondary to the glomerular injury and did not dominate the picture.

As regards the production of chronic changes with diphtheria toxin, there is the difficulty of keeping animals alive for more than a few weeks. Frothingham,¹⁵ in 1914, injected animals repeatedly with sub-lethal doses of diphtheria toxin. He reported failure to produce any significant changes in the kidney with such injections.

With an increasing knowledge of the etiologic factors involved in human glomerulonephritis, especially the acute form, it was but natural that bacteria or their toxins be employed in experimental production of nephritis. All will admit that scarlet fever, bacterial endocarditis and severe sore throats are often followed by glomerulonephritis. The organism involved is probably of the streptococcus group—sometimes the hemolytic type, sometimes the anhemolytic or viridans variety. Experimenters have employed various organisms in the attempt to produce kidney lesions. Some have reported successful results, others have been guarded in their opinions, and a few have confessed failure or, at least, skepticism in their interpretation of the facts.

Le Count and Jackson,¹⁶ in 1914, studied the effect of streptococci on the rabbit's kidney. Fifty-eight animals were given a single injection of living organisms—hemolytic streptococci, from cases of streptococcus sore throat in fifty-one rabbits. In ten animals, no changes were found. In sixteen, acute changes were seen: bacterial emboli in the capillaries, areas of necrosis in the pyramids, acute disorganization of the glomeruli with fibrin thrombi and hemorrhage in some glomerular spaces in only one animal. Apparently, the lesions in the glomeruli healed. Subacute changes were noted in thirty-two rabbits, in the form of lymphocytic and plasma cell exudates about the veins. In twenty-two animals, there were chronic changes—focal scars with dilated tubules, retention cysts and focal regenerative changes. These chronic changes would be rather difficult to distinguish from the "spontaneous" nephritis described by Le Count and Jackson in their article.

Klotz¹⁷ in 1914, injected thirty-four rabbits from one to five times over a period of from two to 228 days with *Streptococcus viridans*.

15 Frothingham J M Research **30** 365, 1914

16 Le Count, E R, and Jackson, L J Infect Dis **15** 389, 1914

17 Klotz Tr Ass'n Am Phy **29** 49, 1914

isolated from cases of endocarditis He described acute and chronic changes in the kidneys, acute and chronic interstitial nephritis, the latter resulting from the former and quite indistinguishable from our present conception of "spontaneous" nephritis Klotz attempted to draw an analogy with the nephritis in man It is perfectly obvious that he was not dealing with a chronic glomerulonephritis

Using *B mucosus-capsulatus*, Major,¹⁸ in 1917, injected twenty-one rabbits Twenty animals showed lesions A single injection in five rabbits produced acute hemorrhagic nephritis (?)—red blood cells in the glomerular spaces, tufts, tubules and interstitium Hyaline fibrin thrombi were seen early in the glomerular capillaries In animals which received repeated injections, marked tubular changes were found, with lymphocytic collections Occasional fibrotic glomeruli were observed In another group, the kidney was granular (pitted?) under the capsule, with numerous areas of round-cell infiltration, dilatation of the tubules and desquamation of the epithelium, fibrosis and destruction of glomeruli Fibrosis around the glomeruli and the early stages of crescent formation were also seen

Winternitz and Quinby,¹⁹ in 1917, injected *B bronchisepticus* directly into the renal artery of dogs They obtained chiefly interstitial changes Involvement of the glomeruli was not general enough to produce marked changes

In 1920, Kuczynski²⁰ inoculated mice repeatedly with streptococci He described glomerular changes, degeneration of the tufts, followed by proliferation and hyalinization All this was considered a defensive process The intermediate stages were not described by the author Hyalinized glomeruli are not uncommon in ordinary mice

In contrast to some of the foregoing results, there was the report of Faber and Murray,²¹ who, in 1917, injected a series of thirty-seven rabbits with various organisms—*Streptococcus hemolyticus* (twenty rabbits), *Streptococcus viridans*, *B coli* and the staphylococcus They failed to produce glomerulonephritis

Pappenheimer and others²² injected hemolytic streptococci directly into the renal artery of the rabbit Only acute changes were produced The micro-organisms disappeared rapidly, through the action of the phagocytes Within a few hours many leukocytes were seen in the glomeruli, and later on suppurative foci appeared, but chronic changes were not obtained

18 Major, R H J M Research **37** 125 (Sept) 1917

19 Winternitz, M C, and Quinby, W C J Urol **1** 139 (April) 1917

20 Kuczynski Virchows Arch f path Anat **227** 186, 1920

21 Faber, H K, and Murray, V J Exper Med **26** 707 (Nov) 1917

22 Pappenheimer et al Proc New York Path Soc **16** 73, 1916

In connection with the foregoing work, the experiment of Bloomfield,²³ in 1919, must be mentioned. He injected dead organisms (*Streptococcus hemolyticus* and *vulgaris*) directly into the left renal artery of rabbits. At this operation, the kidney was examined closely for the presence of "spontaneous" nephritis. About two weeks later, a series of intravenous injections of living organisms was begun, from one to nineteen injections over a period up to fifteen months. The results were entirely negative as regards chronic changes in the kidneys. Of course, Bloomfield was not misled by the "spontaneous" nephritis present in his animals. In twelve of sixteen animals, the kidneys looked exactly the same after as before the injections of bacteria.

Using only bacterial poisons, to rule out the factor of embolism and to make possible more diffuse injury of the kidneys, Stoddard and Woods,²⁴ in 1916, injected toxins obtained from cultures of streptococci and staphylococci, also Vaughan's split-protein poisons. Rabbits were given such injections repeatedly. No glomerular changes of note were produced.

Combinations of a metallic poison, or diphtheria toxin, with bacteria have also been employed in experimental nephritis, with the idea of establishing a site of lowered resistance in the glomerulus, where bacteria or their toxins could then gain a stronger foothold. Following the example of Opie, who, in 1909, found it much easier to produce cirrhosis of the liver in animals by the combined use of chloroform and *B. coli* than by either one alone, O'Hare,²⁵ in 1913, repeatedly injected both uranium and *B. coli* into rabbits. Eighteen of forty animals lived from a few weeks to five months. A varying amount of scarring was produced in the boundary zone and in the cortical rays of the kidney. Lymphocytic infiltration was not marked. The glomeruli were drawn together in the scars and showed variable changes: dilatation of the capsular space, shrinking and thickening of the capsular wall, and, occasionally, proliferation of endothelium. Arteriosclerotic lesions were not found. The fibrosis thus produced was more constant than that found in animals which received only uranium nitrate. Yet all the foregoing results can be duplicated in animals by "spontaneous" nephritis, and, regardless of the origin of the scars, one is not dealing here with a glomerulonephritis. From the latter standpoint, O'Hare's results were negative.

23 Bloomfield, A. L. Bull Johns Hopkins Hosp **30** 121 (May) 1919.

24 Stoddard, J. L., and Woods, A. C. J. M. Research **34** 343 (July) 1916.

25 O'Hare, J. P. Study XVII. Experimental Chronic Nephritis Produced by the Combination of Chemical (Uranium Nitrate) and Bacteria (*B. Coli Communis*), Arch. Int. Med. **12** 49 (July) 1913.

In 1917, Major²⁶ injected young rabbits repeatedly with killed cultures of *Staphylococcus aureus*, over a period of a few months. In each case, a preliminary dose of 0.5 mg of uranium nitrate had been injected. Six of seven rabbits developed well-marked lesions in the kidneys—round-cell infiltration, diffuse fibrosis and varying destruction and fibrosis of glomeruli. No such changes were seen in six rabbits given only the uranium nitrate. The author concluded that chronic nephritis could be produced thus. Grossly, the kidneys showed puckering and scarring. The interpretation of the findings here is somewhat open to question.

In the same year, Faber²⁷ injected ten rabbits with varying small doses of diphtheria toxin, followed in from one to three days by *B. coli*, intravenously. A true fibrinous exudate was found in Bowman's space, some red cells and desquamated epithelium. Frequently, masses of fibrin were seen in the glomeruli. Leukocytes were found in large numbers in the tuft, and occasionally in the capsular space. Early, half-moons appeared. With *B. coli* alone, no notable changes could be produced. Apparently, exudation was more marked when both toxin and organism were used than when the latter alone was employed. With Vaughan's split-protein instead of *B. coli*, similar results were obtained, but there was no leukocytic reaction. While Faber was apparently much more successful than most other experimenters in obtaining a severe exudative type of glomerular lesion, he did not allow his animals to develop chronic changes. They were kept alive for only a few days.

A new phase of experimental chronic nephritis was exposed by Newburgh,²⁸ in 1919. He fed rabbits a high protein diet, egg-white, casein and soy bean representing the protein constituents. Renal injury, shown by albuminuria and cylindruria, was quickly produced. Histologically, the changes were those of acute, subacute and chronic tubular changes, with secondary increase in interstitial tissue. The glomeruli and renal blood-vessels showed little change. The experimental conditions were rather artificial.

In view of the clinical association of acute nephritis with exposure to cold, Gaisböck,²⁹ in 1922, experimented on the effects of direct cooling of the kidneys in animals. Tubular and glomerular degeneration occurred early, but eventually healing took place, and progressive or chronic changes were not obtained in this manner.

26 Major, R H J M Research 35 349 (Jan) 1917

27 Faber, H K J Exper Med 26 153 (Aug) 1917

28 Newburgh, L H Production of Bright's Disease by Feeding High Protein Diet, Arch Int Med 24 359 (Oct) 1919

29 Gaisböck, F Wien Arch f inn Med 3 1 (Nov) 1922

An admirably critical review of the entire field of experimental nephritis was published by Roth and Bloss,⁹ in 1922. They begin with what seems to be the most logical introduction to experimental chronic nephritis namely 'spontaneous nephritis as it exists in various animal species. Veterinary authorities agree on two points the frequency of acute nephritis or nephrosis and the rarity of glomerulonephritis. Henschen³⁰ in 1921 reported the condition of the kidneys of 200 dogs and more than fifty cats on which he performed the necropsy. He stated that degenerative conditions or nephroses were quite common except amyloid degeneration. The most usual form of acute nephritis he called acute interstitial lymphatic nephritis. Here there are lymphocytic infiltrations which later become fibroblastic. Glomeruli atrophy and become hyalinized their capsules thicken and the tubules atrophy, all forming a scar which corresponds grossly to a depression or pit on the surface of the kidney. Renal atrophy of a focal character was commonly found in dogs but produced no symptoms. Arteriosclerotic changes could not be demonstrated. Acute nephritis occurred frequently in puppies.

Roth and Bloss discuss the rarity of true chronic nephritis in animals generally. Thus in 7,000 necropsies on sheep only twenty-three cases of chronic nephritis were found. A true diffuse glomerulonephritis practically never occurred. The authors further draw a distinction between the various degenerative changes described in experimental nephritis and the inflammatory exudative process seen in the true glomerulonephritis in man. They comment on the rarity of exanthems and rheumatic diseases in animals. This factor—the difference in etiology—might explain the differences in the pathologic pictures in man and animals. In ten cases of hog cholera, in some of which a severe endocarditis had occurred no true glomerulonephritis was found. Nor could such a nephritis be produced in rabbits by means of the hog cholera organism. In conclusion they refer to inherent differences between experimental animals and man as a probable cause of the failure to produce glomerulonephritis.

Many of the authors referred to throughout this review of the literature have discussed the so-called spontaneous nephritis as it occurs in rabbits the animals most commonly used. Excellent descriptions have been given by Le Count and Jackson¹⁶ Bloomfield²³ and Bell and Hartzell³¹ not to mention the reports in the earlier literature on experimental nephritis. The characteristic lesions vary according to the stage at which they are observed. In the early stage one finds microscopically a varying amount of round cell infiltration about the smaller

30 Henschen F. Acta med Scandinav 53 774 (Jan) 1921

31 Bell E T and Hartzell J Infect Dis 24 628 (June) 1919

veins, usually in the boundary zone or extending along the vessels upward into the cortex. In the areas of infiltration, the tubular epithelium undergoes necrosis, with resulting atrophy or dilatation of the portion of the uriniferous tubule above the areas. Grossly, one may see no change in the kidneys, but where the infiltration has extended up into the cortex, a plum-colored pin-point or pinhead-sized spot can be seen through the capsule. Eventually, fibrosis sets in, causing distortion of the atrophic or dilated tubules in that area, a drawing together of the glomeruli, and the formation of a narrow or broad wedge-shaped scar which extends from the surface of the kidney down through the entire cortex, causing a depression or pit of varying diameter on the surface of the kidney. The glomeruli are usually shrunken in these scars, but never show anything corresponding to glomerulonephritis. There is occasionally a fibrotic glomerulus. Usually there is, at best, some fibrosis about Bowman's capsule. Within these scars are varying numbers of round cells and degenerating tubular epithelium. These scars are always focal, with entirely normal intervening kidney tissue, and even in extreme cases represent only a minority of kidney tissue. Both kidneys are usually involved to the same extent. In extreme cases, the kidneys may be so pitted and puckered as to give a superficial resemblance to granular kidneys. The capsule is never firmly adherent over these pits. Associated with this cortical scarring may be similar focal scars extending all the way down the medulla.

As regards the frequency with which this condition is found, variable percentages are given in the literature, ranging from about 10 to about 90 per cent. The frequency of "spontaneous" nephritis is, according to Bloomfield,²³ quite independent of the age, size, weight or sex of the rabbit. It is more dependent on the particular lot of animals one is dealing with. But even from 40 to 50 per cent would be a fair average of incidence for most laboratory rabbits.

The etiology is not known. The lesions are apparently embolic in character. Yet, even in relatively late stages, some patent vessel may be seen in the involved area. The rabbit is subject to a sufficient number of infections to make focal embolic lesions possible.

The "spontaneous" nephritis of rabbits has absolutely no resemblance to the human progressive, or chronic, glomerulonephritis. None but a novice in pathologic histology should have any difficulty in distinguishing between the two. Yet a detailed and lengthy description has been given, because, time and again, experimenters have, in all faith, reported, and illustrated with photomicrographs or drawings, what to them was an artificially produced chronic nephritis (comparable to the human type), but what, in the light of present knowledge, could only have been the "spontaneous" variety. Whether or not injections of

bacteria, toxins, or metallic poisons, or what not, can produce scars similar to those occurring "spontaneously" cannot be determined. But it makes no difference either way, because, even if they were so produced, they would represent only a focal chronic nephritis from which the animal would never be in danger of acquiring uremia, cerebral asphyxia or cardiac failure—the Three Fates of human beings with chronic progressive glomerulonephritis.

II. OBJECT OF THIS RESEARCH

Realizing fully the numerous failures in the field of experimental chronic glomerulonephritis but encouraged somewhat by the definite knowledge regarding the injury of glomeruli by certain poisons, and stimulated by the vast importance of the ability to reproduce experimentally, in a constant fashion and under controlled conditions a pathologic process simulating the progressive glomerular disease in man, it was thought worthwhile to undertake the problem, along lines suggested by Prof. H. G. Wells. The object therefore of this research was the production of a chronic glomerulonephritis in an experimental animal. The success of the experiment was to be gauged chiefly by the actual, visible gross and microscopic pathologic changes in the kidneys.

III. METHODS OF PROCEDURE

Several methods were tried:

1. The injection, intravenously of relatively large doses of an organism of low virulence—*Streptococcus viridans* isolated from a "granule" in an infected tonsil which had been removed surgically. This organism was kept growing on blood-agar slants from which it was transferred to tubes of dextrose aspartic broth and grown for twenty-four or forty-eight hours before being used. The contents, from 6 to 10 cc., of these tubes were centrifuged at high speed for a few minutes the culture liquid poured off and the organisms suspended in from 2 to 3 cc. of physiologic sodium chlorid solution, this dose being then injected, every two or three days, into the ear veins of rabbits, as long as they lived. Occasionally, subcutaneous injections were interpreted or substituted.

2. The use of diphtheria toxin, in varying dosage and frequency, in an attempt to cause considerable circulatory disturbance in the kidneys and, thereby, favor the localization and activity in the glomeruli of bacteria present in the blood-stream. The bacteria used were the strain described in the preceding paragraph, and the injections were given in a manner and dosage similar to those there described.

3. The use of ranestake venom in a manner similar to the diphtheria toxin, and for the same purpose, in view of the glomerular injury

toxin in a dosage of from 0.3 to 0.5 of a minimum lethal dose subcutaneously, thirteen rabbits lived less than ten days, nine lived between ten and twenty days, six between twenty and thirty days, four between thirty and forty days, and two, forty-six and forty-seven days, respectively. Some of the animals lost up to two-fifths of their body weight. Most of them lost one-third.

The kidneys showed varying changes. In some animals, a small dose produced tremendous changes. In others, e.g., the rabbit that lived forty-six days and received a total of 2.6 of a minimum lethal dose of toxin, practically nothing was found. In general, there were seen extreme hyperemia and dilatation of the glomerular capillaries, endothelial degeneration, hyaline thrombosis in some of the loops, and, what was very conspicuous but present in only sixteen of the forty-nine animals, globular glomerular hemorrhages into the tuft itself, giving the so-called "blood cysts." There was a varying amount of granular precipitate in the capsular space. Only occasionally were red blood cells seen in Bowman's space. Tubular degeneration was marked and numerous casts were seen in the kidney sections and found in the urine. In spite of all these acute changes, there was no leukocytic reaction to speak of. There was absolutely no proliferative reaction on the part of Bowman's capsule. In some of the animals that lived longer than two weeks, there was evidence of endothelial regeneration in the tuft, but it was not striking.

In four rabbits, a striking picture was seen: a mass of fibrin encircling the glomerulus entirely, or only a part of it, fingering in between the loops of the tuft, at times forming part of an old blood cyst, sometimes entirely within the tuft proper, or else lying free in Bowman's space, with often a hyalinized exudate contiguous with it and extending into the first portion of the tubule as a hyaline cast. This evidently represented an older stage of development than the changes described above, but it was found in animals living seven, sixteen, twenty-seven and thirty-seven days, respectively. Yet no epithelial crescents were ever seen in these kidneys, nor a significant leukocytic reaction.

One animal lived forty-seven days, receiving a total of 4.9 minimum lethal doses of diphtheria toxin and thirteen injections of bacteria. The kidneys of this animal were finely pitted, grossly, and were very firm. Microscopically, there was seen a marked type of "spontaneous" focal scarring. But, in addition to this, there was considerable diffuse interstitial tissue increase, marked variation in the size of the glomeruli, pericapsular fibrosis and connective tissue invasion of glomeruli outside the focal scars and, at times, adhesions between some loop of a tuft and Bowman's capsule. Numerous hyaline casts were present in the tubules and in the urine. The glomerular change here was not general.

enough to be satisfactory. There were no true epithelial crescents. Consequently even here one is not dealing with a true chronic glomerulonephritis, but rather with a chronic interstitial process.

All of the changes described so far have been produced by diphtheria toxin. What about the effect of the bacteria localizing in these injured glomeruli, with their tremendous congestion and hemorrhage? The bacteria seemed to have no effect at all on these glomeruli. There is nothing one could ascribe to their action on the glomeruli. Mycotic emboli were found in many of the glomeruli and in the afferent arteries, in the vessels of the lungs and even in the myocardium, in one animal which had received four minimum lethal doses of toxin intravenously, and the next day when in an almost moribund condition, was given bacteria intravenously, death ensuing in twenty-four hours. There was no reaction about these bacterial masses. Probably, the circulation was in a failing condition when the organisms were injected, and the animal's resistance was nil. In all the other animals, the bacteria had no more effect on the damaged glomeruli than they had on the normal glomeruli of the first series. This result was very surprising, but the objective data were quite convincing.

Twenty-seven of the forty-nine rabbits showed the earmarks of 'spontaneous' nephritis, whether truly spontaneous or not. In seventeen animals, definite focal scars were present. In twelve, grossly visible fine or coarse pitting on the surface of the kidneys was noted, in two of twenty-eight animals that lived less than ten or eleven days, in three of nine rabbits that lived between ten and twenty days, in four of six rabbits that lived between twenty and thirty days, in two of four rabbits that lived between thirty and forty days, and in one of the two rabbits that lived forty-six and forty-seven days, respectively. The other rabbit of the two had microscopic focal scars. Here, again, there is a temptation to draw conclusions, but one must be careful, because pitting occurred in animals that lived only two days and seven days, respectively, while extreme scarring and deformity of the kidneys were seen in an animal that lived only eleven days, obviously too short a period for even an enthusiastic concluder.

Endocarditis of the vegetative type was found in only three rabbits of this series. They lived fifteen, eighteen and forty-seven days, respectively. In the first animal of the three, there was an extensive infarction of one kidney, with multiple glomerular abscesses in that area. In the rabbit which lived eighteen days, a marked aortic endocarditis was present.

Arteriosclerosis was not produced, in spite of the relatively large number of animals used, the large doses of diphtheria toxin given and the considerable period of time many of the animals lived.

3 A series of twenty-six animals received from one to eight injections of rattlesnake venom—a total of from 10 to 66 mg of the poison—subcutaneously. The usual bacterial suspension was injected intravenously, every second or third day. In two animals, a small dose of the venom, given intravenously, caused death within from two to three minutes, after convulsions. The subcutaneous injections always produced an extensive necrosis, particularly of the muscles, even at a great distance from the site of introduction of venom. All the animals lost considerably in weight.

Of the twenty-six rabbits, six lived between one and five days, fourteen between five and ten days, five between ten and fifteen days, and one for forty days. Postmortem changes set in very rapidly in these animals. As regards the kidneys, beyond hyperemia and degeneration of glomerular endothelium, with a granular precipitate in Bowman's space in some instances, there were no significant glomerular changes. This was surprising in view of the hemorrhagic and exudative lesions described by some authors.

Nine of the twenty-six rabbits showed evidence of "spontaneous" nephritis, but only one animal had kidneys which were extremely scarred and pitted grossly. Yet this animal had lived only nine days after the beginning of the experiment, so that one could not very well blame the experimental procedure for the pathologic condition found.

Mitral endocarditis was present in three rabbits, which lived four, eight and thirteen days, respectively. There were only a few small vegetations in each instance.

4 Direct intracardiac injections of a strain of *Streptococcus viridans*, isolated from the blood of a patient with subacute bacterial endocarditis, were carried out on ten rabbits. Two of these lived less than ten days, six between ten and twenty days, and two, twenty-four days. The number of injections varied from three to nine. The cause of death in all the animals was a more or less gradual deposition of layers of clotted blood within the pericardial cavity, distending it tremendously. Within these clots were masses of bacteria in microscopic abscesses. Four rabbits developed a definite vegetative endocarditis, never ulcerative in spite of the trauma to the endocardium during the repeated injections. The endocarditis was present only in animals that lived more than ten days, and in 50 per cent of these.

The kidneys showed no more changes than those in the animals of Series 1. No glomerular lesions of any sort were encountered. In one of the rabbits that developed endocarditis, a small infarct was found in one kidney. In this series of ten animals, only two showed spontaneous nephritis. In only one was gross pitting evident.

5 Direct injection of a bacterial suspension (the same organisms as in Series 4) with lycopodium spores into the left renal artery was carried out on twenty-six animals successfully. They were allowed to live from nineteen to sixty-five days, when they were killed by a blow on the back of the neck, and necropsy was performed immediately. Most of the animals maintained their body weight and some actually gained following the operation. No injections were given other than the one into the renal artery. Five rabbits lived less than ten days, and in all of these, the left kidney was more or less completely infarcted owing partly to injury to the vessels at operation and partly to obstruction of branches of the renal artery by masses of spores that had clumped together. Two animals lived just a little less than twenty days. Seven lived between twenty and thirty days, two between thirty and forty days, two between forty and fifty days, four between fifty and sixty days, and four between sixty and sixty-five days.

The kidneys, i.e., the injected kidneys, of the animals in this series showed, in general, uniform findings. Leaving out the presence of large infarcts, due to faulty technic or obstruction of large branches of the renal artery by masses of spores, the kidneys showed, grossly, a varying amount of pitting or coarse depressions, with wedge-shaped cortical scars. Microscopically, wedge-shaped areas were found in the cortex, with relatively wide bases, in which were seen tubular degeneration, atrophy and distortion, marked fibrosis between the tubules and around the glomeruli, often large masses of round cells near a vessel containing spores and an organized, canalized thrombus, and a varying number of spores in the arterioles, very rarely in a glomerulus. The spores were just large enough to obstruct the afferent vessel of the glomerulus, but too large to get in the capillaries. Between these areas of scarring, little change was evident, other than the focal scars of spontaneous nephritis, which could be distinguished only with great difficulty from those due to the spores and bacteria. In fact, in many instances, only the finding of spores in the vessels was the differential point. In some kidneys, the findings were frankly those of multiple organized or organizing infarcts, with tremendous interstitial fibrosis. Within these areas, the glomeruli themselves showed little or no change, even in cases in which a spore was present in the glomerular capillary. Pericapsular fibrosis was marked.

All these changes could be attributed to partial or complete obstruction of arteries to the involved areas. In other words, this was a focal embolic process, the obstruction being due to the inert spores. The bacteria apparently played no important rôle—not any more than in Series 2, in which organisms and diphtheria toxin were injected into the rabbits. The only lesion that could be attributed to bacteria was the

tremendous focal lymphocytic accumulation seen about some of the small vessels in the cortex and sometimes in connection with a glomerulus. This lesion was not seen in a rabbit which had received only spores in sterile physiologic sodium chloride solution, although the usual scarring was present.

While one could not tell, in the case of the left kidney, how much of the pitting was due to the treatment and how much was spontaneous, the analysis of the findings in the opposite, untreated, control right kidney gave interesting results. Fourteen of the twenty-six rabbits showed a varying amount of gross pitting, in the right kidney. Three more showed microscopic scars and round-cell infiltration—making a total of seventeen of twenty-six which had spontaneous nephritis, unless the findings could be attributed to the effect of circulating bacteria, originally injected into the opposite kidney. But this explanation could not possibly hold for the extreme scarring and puckering of the kidneys of two rabbits that died during the operation. Nor could it explain the pitting found in the right kidney of the rabbit which received only spores. Whatever the cause of the pitting in the right kidneys, the incidence was unusually high in this series.

The bacteria injected into the left renal artery produced a definite vegetative endocarditis in four rabbits, which lived five, eighteen, nineteen and twenty-seven days, respectively. In the first animal, there were microscopic embolic abscesses in the myocardium. In the second animal, there were focal leukocytic infiltration in the myocardium and an infarct in the right, or untreated kidney.

6 During the course of the various experimental procedures carried out above, a simultaneous study was made of the histologic condition of kidneys obtained from rabbits which happened to die in the laboratory. Some were unused rabbits, supposedly normal. Most of them had been injected with human serum, lens protein, etc., in the course of work on precipitins. None had received bacteria of any sort.

A total of eighty-two kidneys (forty-one rabbits) were studied. Forty-eight kidneys (twenty-four rabbits) were entirely normal, thirty-four showed a varying amount of focal cortical scarring, round-cell infiltration, etc. In many of the thirty-four, gross pitting was present. Thus, more than 40 per cent of these rabbits showed spontaneous nephritis. This is an important phase of the work on experimental nephritis in the rabbit.

V SUMMARY

A critical, yet, we trust, a fair review of the literature on experimental chronic glomerulonephritis shows that many investigators have reported successful results that cannot stand when viewed in the light of strict criteria for glomerulonephritis. But many who have made

careful and extensive experiments have failed completely to produce chronic renal lesions comparable to the typical chronic glomerulonephritis of man. Not all the workers have seemed to distinguish between "spontaneous" nephritis and the true form of chronic glomerulonephritis which ends in the so-called granular or contracted kidneys.

The present attempt to produce glomerulonephritis, by injection of bacteria repeatedly, of bacteria and diphtheria toxin, of bacteria and snake venom, of bacteria and spores directly into the renal artery, has met with absolute failure. Many pathologic processes have been described in the protocol, but none of these is a true glomerulonephritis. Yet the bacteria were able to produce vegetative endocarditis (never ulcerative) in a fair proportion of the animals.

"Spontaneous" nephritis was found in 40 per cent of rabbits which had never received bacterial injections. In seventy-two of 133 rabbits used in the experiments of this research, spontaneous nephritis was noted, whether spontaneous or not cannot be decided. In other words, 54 per cent had the typical lesions, which, however, are very easy to distinguish from those of glomerulonephritis.

VI CONCLUSION

Chronic glomerulonephritis has not yet been produced constantly or even frequently in an experimental animal. The rabbit is probably not a suitable animal for this purpose, because it does not react as does the human being to the agents that can injure the glomeruli. My own attempts to produce a chronic lesion by means of bacteria alone, bacteria with diphtheria toxin, bacteria with snake venom or bacteria with spores, all calculated to damage the circulation within the glomeruli and introduce infection at the same time, have been unsuccessful, although a large number of animals were used with each method of procedure. Whatever changes were observed in the kidneys could not be interpreted as those of chronic glomerulonephritis.

HEMATOPORPHYRINURIA AS AN INDEPENDENT DISEASE ("HEMATOPORPHYRIA") AND AS A SYMPTOM OF LIVER DISEASE AND INTOXICATIONS *

FRANCIS HARBITZ, MD

CHRISTIANIA, NORWAY

Among the so-called autointoxications, there is a group, not very well defined, characterized by a constitutional defect which prevents the complete decomposition of certain substances. As a result, intermediate metabolic products accumulate in the blood and internal organs, and at times well defined morbid conditions, even death, may result.

Such conditions have long been known, among them being arthritis urica, diabetes mellitus the comparatively unimportant cystinuria and alkapttonuria. The last named condition is now well known, chiefly since the appearance of a monograph by the Danish investigator Valdemar Poulsen.¹ Its sequel, ochronosis (blackening of cartilage and other tissues), had already been described by Virchow, and, on account of its rarity and harmlessness, may be considered a pathologic curiosity.

Of greater practical and theoretical importance is hematoporphyrinuria, so named on account of the presence in the urine of a light reddish brown pigment, best known to occur in connection with poisoning by sulphonmethane and sulphonethylmethane. Less known is the fact that hematoporphyrinuria may be the expression of a constitutional state, "porphyria," or "hematoporphyrinia," an exceedingly interesting condition with a fairly well defined morbid anatomy, and recently the subject of a monograph by Hans Gunther.²

REPORT OF CASES

CASE 1—*History*.—A hostler, aged 43, had been under the observation of Prof Peter Bull for many years. In 1903, when 28 years old, he had two months of diarrhea with rather scanty, painless and at times bloody stools. This was followed by constipation. There was no jaundice. The following year he was in bed a week with fever, vomiting and pain in the right hypochondriac region, radiating to the back. He had a similar attack in 1905, and was never entirely well, being frequently troubled with nausea, poor appetite and pain in the right side. In 1906 and again in 1910, he had similar attacks. In 1910, it was noted that the urine was dark, with light colored foam, and free from sugar and bile pigments. The addition of iodin caused it to be more intensely brown (not green). Nov 3, 1910, laparotomy was performed and the appendix was removed. The biliary tract was normal. Nine days later, he had an attack of pain during which the urine was dark and contained urobilin and hematoporphyrin. The action of the bowels was normal.

* From the Department of Pathology, University of Christiania

1 Poulsen, Valdemar Om ochronotiske tilstande hos mennesker og dyr, 1910

2 Gunther, Hans Die Bedeutung der Haematoporphyrine in Physiologie und Pathologie, 1922

November 15, the muscular power in the arms was much reduced and the grip weak, and there was distinct atrophy of the thenar eminences. Sensation was normal. The abdomen was constantly tender.

November 23, on neurologic examination by Dr. Eyvin Krogh, evenly distributed paresis of both arms and legs was found. The tendon reflexes were absent, sensation was normal, the eye grounds were normal, the urine was yellow. Retention of urine was present for a month, and the weakness of the extremities lasted a year. It was thought that there was an acute affection of the anterior horns or roots of the cord, extending at least as high as the fifth cervical segment, the cause being an intoxication or infection.

Further Observations (Dr. Andreas Tanberg)—From 1911 to 1913, the patient improved considerably, and he became able to walk about by the aid of a cane. In the fall of 1916, he grew weaker, and in March, 1918, he was confined to bed. He complained of pain here and there in the arms and legs. Once or twice a year, he had peculiar attacks of abdominal pain, lasting about a week, and less severe in recent years. The onset was usually sudden, and the pain was usually in the umbilical region. The patient had the impression that the pain started on the right side. There was no distension, and tenderness was not pronounced. The pains, which were stinging and burning, were usually accompanied by vomiting of watery and, toward the end, bile-stained material. The urine was of light color on the first day of the attack, but grew darker from day to day and the dark color, the shade of Madeira wine, persisted for several days after the cessation of pain. The temperature was always normal, the pulse rate from 80 to 100. The skin and sclerae were slightly icteric during the period of excretion of dark urine.

During one of the attacks in 1911, there was tenderness and swelling of both breasts, and the lightest touch of the nipples caused pain. The liver was not enlarged during the attacks. Spectroscopic examination of the urine revealed large quantities of urobilin and urobilinogen, together with a trace of hematoporphyrin. In the later years, the skin and sclerae were constantly slightly yellow. In 1916, he began to have frequent attacks of vertigo, with vomiting and sometimes fainting. The same year, there appeared a slight paresis of the muscles of the right side of the face. Signs of chronic nephritis were present during the last five or six years of his life, the urine containing from 0.5 to 1 per cent of albumin, granular and hyaline casts, a few leukocytes and a very few erythrocytes. During the last eighteen months, albuminuric retinitis had been present.

The patient had used alcohol only moderately. In 1910, a negative Wassermann reaction was obtained.

Outcome—April 16, 1918, the patient was admitted, in a comatose condition, to the service of Prof. Peter F. Holst. A week previously, one of his usual painful attacks had come on, and from day to day, consciousness became more clouded. There was no fever, but the pulse rate was 120. The area of cardiac dulness was slightly increased. Atrophy of the musculature of the hands, forearms and legs was noted. The urine contained a considerable quantity of albumin and casts. The patient died April 18.

Necropsy Findings (April 18)—The body was that of a man who appeared older than his chronological age. There were numerous punctate hemorrhages on the radial side of the right forearm. The musculature of the thenar and hypothenar eminences, forearms and legs was considerably wasted. The pericardial cavity contained clear yellow fluid, and its layers were smooth. The heart was enlarged, weighing 450 gm., and the wall of the left ventricle was thickened and its cavity dilated. There were a few sclerotic patches in the coronary arteries, but no narrowing of their lumen. Otherwise, the heart was normal. The pleural cavities were normal as were the lungs, aside from slight hypostatic congestion. There were some fibrous adhesions about the gallbladder. The spleen was enlarged, weighing 135 gm., and rather firm, and its follicles

were indistinct. The kidneys were also rather large with adherent capsules and presented, on cut surfaces, numerous cysts and yellow patches. The line of demarcation between cortex and medulla was entirely effaced. The liver was rather small, weighing 1,100 gm., and somewhat cyanotic, with indistinct markings. The gallbladder and ducts were normal. The stomach, intestines, pancreas and bladder showed no changes. The skull and dura mater were normal. The brain was large and edematous, with broad gyri and narrow sulci. The vertebral arteries were thickened and tortuous, with sclerotic patches in their lining. The basilar artery was still more dilated and also sclerotic, with a thrombotic mass which almost filled the lumen in its lower portion. Corresponding to the thrombus, there was softening in the lower portion of the pons. There were also small foci of softening on the right side of the cerebellum, at the tip of the left caudate nucleus and in the wall of the third ventricle. The small arteries at the bottom of the cerebral sulci were sclerotic. The spinal dura presented in the cervical region a fibrous thickening up to 3 mm. of the consistency of scar tissue, as well as brownish pigmentation. The cord itself was slightly swollen in the cervical region and the demarcation between the gray and the white matter was not distinct. The white matter appeared somewhat degenerated. The same was true to a less degree of the rest of the spinal cord.

Histologic Examination.—Kidneys. There was marked degeneration of the epithelium of the convoluted tubules, which was partly shed. The lumina of the tubules were narrow in places, in other places dilated, and partly filled with homogeneous material. The stroma was considerably increased in both the medulla and the cortex, in the latter, this occurred in areas in which the epithelium was much degenerated and partly destroyed. There was some round-cell infiltration in the cortex, and the glomeruli were largely converted into hyaline lumps in which degenerated nuclei were seen. The walls of the larger vessels were somewhat thickened.

Liver. This showed parenchymatous degeneration.

Brain. In the cortex of the cerebrum, as well as in the underlying white matter, there was abundant yellowish brown granular pigment around both veins and arteries. The brain tissue was edematous, most distinctly so about the vessels. Yellow pigment was also found in the meninges. These findings were less marked in the basal ganglia, and scarcely recognizable in the cerebellum. There was no sign of inflammation anywhere and no marked change in the ganglion cells. The arteries of the base especially the basilar artery, showed considerable intimal proliferation with slight cell infiltration, considerable pigmentation in the deep portion of the wall and deposits of lime salts. There was a conspicuous swelling from edema of the vascular walls, with a reticular appearance, and, in other places, hyaline degeneration was present. There was practically no inflammatory change about the vessels.

Spinal cord. The changes were not marked. There was no inflammatory infiltration in either the membranes or the cord substance. Slight edema was present in the cervical region but not elsewhere. The ganglion cells were normal, except for questionable atrophy of portions of the anterior horns in the upper cervical region.

Peripheral nerves. The sciatic, ulnar and radial nerves gave no evidence of inflammation, but there was some granular degeneration of the myelin sheaths and axons. Marchi preparations were not made.

Anatomic diagnosis. Porphyrinuric autointoxication (?), chronic nephritis with atrophy, hypertrophy of the heart, chiefly of the left ventricle, arteriosclerosis, particularly of vertebral and basilar arteries, thrombosis of the basilar artery, softening of a portion of the cerebellum and pons, wall of third ventricle and left caudate nucleus, edema of the brain, myelitis of cervical region of cord (?), spinal pachymeningitis with pigmentation, atrophy of the musculature of the upper and lower extremities, and parenchymatous degeneration of the liver.

Comment—The findings in this case agree quite well with those described during the past ten years as porphyria or hematoporphyrin acuta. About twenty cases have been reported, and most of them are assembled in the previously mentioned monograph by Hans Gunther. Recently, additional cases have been reported by Snapper.³ The acute form of the disease has affected women in about two-thirds of the cases, and in about one-third of the cases there has been a neuropathic or psychopathic basis. There is a triad of symptoms, consisting of intestinal colic, vomiting and obstinate constipation. Attacks of abdominal pain occur without demonstrable reason. The pain usually begins in the epigastrium and often radiates to the loins or to the lower extremities. Epigastric tenderness may be present. Vomiting occurs in 90 per cent of the cases. The clinical picture may thus resemble appendicitis, gallstones, kidney stone or ileus. There is usually retention of gastric contents, with dilatation of the stomach and upper part of the small intestine, in other words, symptoms pointing to partial obstruction in the intestine, which has been interpreted as spasm of the duodenum or upper ileum. We may also see the picture of acute dilatation of the stomach or duodenum. The vomitus is often bile-stained. To this condition is added obstinate atonic constipation, with small lumpy stools and bloody mucus. Vesical tenesmus may occur. Fever has been present in half of the cases.

The blood examination reveals normal conditions. The blood serum does not, as a rule, contain hematin or hematoporphyrin, and there are no signs of hemolysis.

The characteristic feature is the abnormal condition of the urine during the attack. It assumes a reddish brown, port wine or malaga color, and, on spectroscopic examination, it is found to contain hematoporphyrin, namely, uro- and enterohematoporphyrin. Urobilin and urofuscin may be found in the urine, which usually is very acid and scanty. In one-third of the cases, albumin and casts have been found. Suga, hemoglobin, hematin and bilirubin are not present.

The attacks mentioned usually occur several times a year, as in Case 1. A whole series of nervous symptoms gradually appear sensory disturbances, neuralgic pains, insomnia, the presence of hyperesthetic zones, psychoses, epileptiform attacks, deliria and, finally, mild polyneuritic symptoms, such as radial or ulnar palsy with tenderness of these nerve trunks. Complete paralysis and sometimes amaurosis may develop. Ascending paralysis has been described in about 50 per cent of the fatal cases. Toward the end, in addition to paralysis of the extremities, paralysis of the sphincters, vocal cords and ocular muscles may set in, and the tendon reflexes disappear. Death usually occurs a few weeks after the onset of an acute attack.

³ Snapper, I. *Deutsch med Wochenschr* 48: 619 (May 12) 1922.

The postmortem findings have been relatively few and ill-defined. There has usually been degeneration of the liver with "siderosis." The bile is dark. In the kidneys, there are usually fatty degeneration and hyperemia. Chronic nephritis was found in one instance. Brownish red granular pigment is found in the epithelium of the renal tubules. Degeneration of the pancreas has been described, and in the stomach and intestine, erosions and hyperemia. In the large intestine, coating with mucus and pus has been found. Siderosis of the spleen sometimes is present.

The greatest attention naturally has been given to the nervous system, both central and peripheral, but as yet the findings have been few, inconstant and indefinite. There seems to be agreement on the absence of inflammatory alterations. Marked and widespread degeneration of the ganglion cells of the anterior gray horns of the cord and spinal ganglia has been met with, though relatively seldom. In other cases, there have been degeneration of peripheral nerves and corresponding muscular atrophy.

As to the deposition of hematoporphyrin in the tissues, there has been practically no investigation which would be of interest, particularly in connection with cartilage and bone.

The findings in our own case contain many points of interest, particularly in the absence of inflammation and degeneration of brain and cord cells, while the presence of parenchymatous degeneration of nerve fibers points to such nerve degeneration as the cause of the marked muscular atrophy encountered. Of further interest is the pigment deposit in the walls of the cerebral vessels and in the membranes of the spinal cord, the latter associated with fibrous thickening of the dura in the cervical region.

The second group of changes which dominates the anatomic picture consists of the severe arteriosclerosis and nephritis. The arteriosclerosis was general, but most pronounced in the brain, where it led to dilatation and secondary thrombosis of the basilar artery, which was the immediate cause of death. I consider it reasonable to suppose that the arteriosclerosis is part of the disease, as there was pigmentation as well as proliferation in the arterial walls and because arteriosclerosis is a prominent feature of other auto-intoxications. I have previously pointed this out in connection with affections of the parathyroids, abnormal calcification and osteomalacia.⁴

The chronic nephritis with atrophy should also be looked on as a link in the disease. Both it and the arteriosclerosis are the expression

⁴ Harbitz, Francis. Pathologiske fund i hypofysen og glandulae parathyreoidea, 1916, Et tilfælde af osteomalaci med svulst av gland parathyreoidea, 1915.

of a long continued effect on the tissues of injurious toxic substances⁵. The liver degeneration is probably also of great importance for the whole clinical picture.

In acute cases, the clinical picture, as well as the anatomic findings, may be quite different. Through the kindness of Dr N. B. Grondahl, I am able to relate the following case, observed by him nearly twenty years ago.

CASE 2—History—A woman, aged 27, a robust domestic, admitted to the Stavanger Hospital, Dec 31, 1904, about December 15 had complained of fatigue and loss of appetite. This was followed in a few days by pain in the right iliac fossa, and within a week by severe pain under the left costal arch, with some tenderness. December 30, she had a sudden attack of unconsciousness with clonic spasms, dilated pupils, and opisthotonus. A similar attack occurred the following night. Between the attacks, she was stuporous and did not respond to questioning.

Examination—On admittance, she was rather restless, with a pulse of 140, and with some general impairment of sensibility. There was no trace of paralysis. The urine was yellowish red, and the coloring matter could not be extracted by chloroform.

Course—Jan 1, 1905, there were five attacks of unconsciousness, the first four very brief, the fifth one of fifteen minutes' duration, with clonic spasms of the right half of the body. January 4, she was very restless and had hallucinations of sight. Hypnotics were required to produce sleep. Fever was present. January 8, she was very dull and had involuntary discharges. The urine, which was dark brownish red, contained no albumin, sugar, or blood. January 13, the urine had become Burgundy red. The patient was very weak and pale, and, January 15, she became cyanotic and completely apathetic. The blood serum was not discolored. Cheyne-Stokes breathing developed, and she died, January 16. Urine obtained during the last few days of life was sent to the Physiologic Institute, and Professor Torup reported that it contained "hexahydrohematoporphyrin, a reduction product of hematoporphyrin produced by liver degeneration."

Necropsy (Dr Grondahl)—The meninges and brain were normal. Hemorrhages were seen in the epicardium and beneath the endocardium on the right side. The heart was soft and small. The lungs were normal. The liver was small and very soft, almost mushy. The cut surfaces were yellowish brown with indistinct markings. The spleen, kidneys, stomach, intestines and genitalia showed no gross changes.

Histologic examination of the liver revealed degeneration of all liver cells, and there were numerous yellowish brown pigment granules, especially in the peripheral portions of the acini and in the vessels. The epithelium of the biliary tract was normal. A diagnosis of subacute liver degeneration was made. In the kidneys, there was degeneration of the cortical epithelium and in both cortex and medulla the epithelium and interstitial tissue contained numerous pigment granules similar to those seen in the liver.

Comment—The striking feature of this case was the early appearance of cerebral symptoms which evidently depended on the hepatic disease. The abnormal condition of the urine was first observed at about the middle of the disease, the urine gradually growing darker.

⁵ Recently, Kleinschmidt (Frankfurt Ztschr f Path 28, 1920) reported a case of endogenous ochronosis with alkapturia, in which both arteriosclerosis and chronic nephritis existed.

on account of the presence of hematoporphyrin. It is reasonable to consider the hematoporphyrinuria as a symptom of the whole disease, particularly of the liver affection. In many ways, this case differs from other cases of hematoporphyrinuria. Anatomically, it most closely resembles acute yellow atrophy. The cause of the disease is obscure.

In addition to the idiopathic constitutional form we have an acute toxic hematoporphyrinuria. This is best known as occurring after the prolonged use of sulphonmethane, and has been most frequently observed in women. However, as only a few patients taking this drug develop hematoporphyrinuria, we must assume a special predisposition, probably dependent on physical and mental depression. Serious cases have been observed after the ingestion of from 10 to 20 gm. The symptoms resemble those described for the idiopathic form, with the triad of intestinal colic, vomiting and constipation. Later, pigmentation of skin and mucous membranes is observed. Most characteristic, of course, is the condition of the urine such as has been described. Nervous symptoms, as neuralgic pains, paresthesias, palsies, and sometimes terminal ascending paralysis make their appearance. The mortality, according to Gunther, is 90 per cent, but this figure is probably much too high. The duration has varied from four to ten days. Anatomically, degeneration and pigmentation of the liver have been found, sometimes also swelling and pigmentation of the spleen, toxic neuritis and scattered degenerations in the central nervous system. The manner in which sulphonmethane produces hematoporphyrinuria is not known.

Following is a case of this kind, but with urobilin in the urine.

CASE 3—History—A woman, aged 21, was admitted to a hospital in May, 1908, with a diagnosis of hysterical insanity. At the age of 16 she had been treated for an abdominal disease, probably tuberculous peritonitis. Later, she developed obstinate diarrhea and cystitis, with foul urine. For a time, albuminuria was present, disappearing in March, 1904. Later, the patient was troubled with constipation, dyspeptic symptoms and, a few times, vomiting of blood. She often complained of headache, and for seven or eight years, she had been subject to attacks of hysterical laughing and crying. During an attack of restlessness with hallucinations in March, 1908, she had been given barbital on fifteen occasions. May 6, she was admitted to another hospital where she was given barbital, sulphonmethane, paraldehyde and hyoscine. On account of the appearance of a morbilliform eruption, barbital was discontinued. May 16, the urine became red, and hematoporphyrinuria was suspected, but Professor Torup found the abnormal substance to be urobilin. The patient became apathetic, and developed slight fever with sluggish pupils and loss of knee reflexes. Otherwise, there were no definite physical signs. She died, May 22. During the period from May 16 to 18, she had taken a total amount of 10.5 gm of sulphonmethane, 1.5 gm of barbital, 10 cc of paraldehyde, and about 2 mg of hyoscine. No hypnotic was given later than May 19. The urobilinuria lasted seven days.

Necropsy—There were no changes of the skin, meninges, brain, heart or lungs. The liver was small (820 gm) soft and dark, with a yellowish green olive-like tinge, with dark and indistinct markings. The bile ducts were normal. The spleen was also small (80 gm), rather dark and soft. The kidneys weighed

200 gm., and were firm with adherent capsules, indistinct markings and closely set yellow stripes in the cortex. The urinary bladder was normal. There were old adhesions about the ovaries and tubes, but no signs of active tuberculosis. The stomach and intestines were normal.

Histologic examination of the motor area of the brain revealed no definite changes. The peripheral nerves were not examined.

The main feature was the liver degeneration, which was in a stage of transition to acute yellow atrophy. The chronic nephritis is also of importance.

Similar cases of poisoning have been observed after prolonged use of sulphonethylmethane. Eleven cases have been reported. Chronic lead poisoning also has been considered a cause of hematoporphyrinuria, and the presence of urobilin in blood and urine, pigmentation of the skin, cirrhotic changes in the viscera, colic and polyneuritis are recognized features of lead poisoning. In a recent study of industrial lead poisoning a Danish physician, Tage Plum⁶ found hematoporphyrinuria to be very frequent. In control examinations of seventy other patients, Plum found hematoporphyrinuria in one case of cirrhosis with marked icterus, and in a patient with hemolytic icterus.

Among other poisons said to have caused hematoporphyrinuria are barbital, phenobarbital, acetanilid and nitrobenzene.

An interesting case of hematoporphyrinuria ascribed to chloroform was reported from Norway in 1901 by Johan Nicolaysen.⁷

CASE 4—History—A woman, aged 29, came to the hospital in January, 1900, with supposed appendicitis. The urine was dark yellowish brown, of specific gravity, 1.039, contained no albumin, sugar, bile pigment or blood, and gave a red ring with Heller's test. The patient was discharged as recovered in a few weeks, but some days later she complained of pain in the back and right iliac fossa. In April, she had a sudden attack of epigastric pain with intestinal colic, vomiting and constipation, and no particular tenderness at McBurney's point.

Operation and Course—May 1, the appendix was removed, and was said to show signs of chronic appendicitis. The next day, the urine was reddish brown, of specific gravity 1.035, and contained hematoporphyrin. The patient recovered promptly. Four months later, the urine was reddish yellow and acid, of specific gravity 1.026, and contained urobilin. In October, 1923, Professor Nicolaysen reexamined the patient and learned that she had had no more colic or constipation, but that the urine had remained dark for many years. Until ten years ago, she had frontal headache, with vomiting every week, and during these attacks, the urine was usually dark. Now the urine was light yellow, of specific gravity 1.015, and contained no albumin, sugar or pus.

Comment—It is reasonable to assume that this was a mild case of hematoporphyrinuria and that the alleged appendicitis really was an attack of the forme fruste. The chloroform naevosus appears to have rendered the hematoporphyrinuria manifest. Noteworthy is the subsequent transition to urobilinuria and the good state of health of the patient in later years. We may here have a porphyria with good

⁶ Plum, Tage Nord Hyg Tidskr **2** 191, 1921.

⁷ Nicolaysen, Johan Norsk Mag f Lægevidensk **24**, 1901.

prognosis, a condition of which we know almost nothing, but which may be more common than we think

A chronic form of hematoporphyria has been described, but it is rare and even of doubtful identity. It is familial and congenital, becoming manifest in late childhood or at middle age and occurring in paroxysms with long or short intervals, often with intestinal prodromes. It is particularly characterized by cutaneous lesions after exposure to light. These consist of erythemas, vesicular formations, often marked pigmentation, and typical *hydrea aestivale* or *vacciniforme*. Some hours after exposure to light, especially in spring or summer, there appear on the unprotected portions of the face and hands, the sensation of heat, itching and formation of vesicles, sometimes with bloody contents. Coryza, conjunctivitis, edema and diarrhea may be associated, the attack usually lasting from two to five days, during which time the urine becomes reddish brown and contains hematoporphyrin. The cutaneous symptoms have been ascribed to deposition of hematoporphyrin in the skin. Subsequently, the skin may remain thickened, the condition resembling scleroderma.

Thirteen cases have been reported as congenital hematoporphyria. They were characterized by repeated attacks of eruption after exposure to light, with associated hematoporphyrinuria, as well as the presence of urobilin and urofuscin in the urine. Pigmentation, erythemas and vesicle formation, even with pus, occur, and subsequently, cicatrix formation and mutilation of the nose, eyes, ears and fingers. The latter become atrophic, often ankylosed, with deformed nails, and whole phalanges may be lost. Hence, the affection may closely resemble leprosy or syringomyelia. It is said that the disease, in part, occurs when the patient is neuropathic, and in individuals with a tendency to pigmentation and strong growth of hair. The eyes may be the seat of yellowish pigmentation, severe conjunctivitis and, later, keratitis and iritis, with resulting ulceration, leading to blindness. Enlargement of the spleen may exist, but symptoms on the part of the nervous system are lacking, and the blood picture is normal. Anatomically, we may find a large, brownish red spleen with abundant pigmentation, as well as a cirrhotic and pigmented liver, while the kidneys are free from pigment. Pigmentation is also found in the bones and the cement of the teeth, especially in a case reported by Hegler, E. Frankel and Schumm.⁸ The cranium, sternum, and ribs were brown, the cartilages white.

AFFECTION OF ANIMALS

In otherwise healthy cattle, horses and hogs, a condition has been described which seems to be identical with, or at least closely related

⁸ Hegler, Frankel and Schumm. Deutsch med Wchnschr., 1913, p 18

to human hematoporphyrinuria. This is the so-called ochronosis characterized by reddish brown or chocolate brown discoloration of the bone tissue. The cartilage is not involved, while in human beings the reverse is true the cartilage being blackened while the bones are normal. The color depends on deposits of substances one of which, according to the chemical and spectroscopic properties, is hematoporphyrin. The condition is rare and has not been closely studied. To my knowledge no case has been observed in Norway. Alexandra Ingier⁹ while working with Schmorl in Dresden, studied the affection in an ox and a hog and found a pigment which proved to be a hematoporphyrin. She looks on ochronosis as a metabolic disorder dependent on certain enzyme activities.

GENERAL COMMENT

The essential feature being the presence of hematoporphyrin in the urine we will describe this substance in further detail. When produced artificially from hematin it is reddish violet, but if in a strongly acid solution, it is of a purple hue. It is insoluble in water and weak acetic acid sparingly soluble in ether and chloroform and soluble in alcohol in dilute acids and alkalis. In glacial acetic acid, it dissolves with formation of thin rhombic reddish brown crystals. It has no definite chemical reactions, but a typical spectroscopic picture. To observe the latter, it is customary to extract with alcohol containing a little hydrochloric acid or by shaking the urine with equal parts of acetic ether with addition of a little 30 per cent acetic acid (Saillet's method). In legal medicine, spectroscopic examination for hematoporphyrin is used in the examination of suspected blood stain in decomposed material extraction with concentrated sulphuric acid for fifteen or twenty minutes being employed. We do not as yet know what hematoporphyrin really is and where and whereof it is formed. It is generally thought that it is formed from hemoglobin by the splitting off of the iron for it is free from iron. Its chemical formula is generally given as $C_{16}H_{18}N_2O_3$ or $C_{34}H_{38}N_4O_6$. Experimentally, it is readily prepared by treating hematin with hydrobromic acid and glacial acetic acid, and this is the "porphyrin" the solutions and spectrum of which are described in technical works.

It was thought that this "genuine" hematoporphyrin was identical with the coloring matter found in the urine in the diseased condition described by us but the matter is not so simple. We have gradually learned that there are several porphyrins in addition to the artificial one, a urohematoporphyrin and an enterohematoporphyrin or coprohematoporphyrin are found in the urine in this disease. The last named substance can be obtained also from the stools when much blood

⁹ Ingier, Alexandra Ziegler's Beitr 25 199 1911

is given in the food as it forms during the decomposition in the intestine, but it is not absorbed and does not seem to play any important rôle (Hans Fischer¹⁰)

What is the source of the porphyrin found in the urine and blood in the disease porphyria? There is apparently no destruction of red cells with decomposition of their coloring matter, and hematoporphyrinuria does not occur in connection with hemolysis nor in hemoglobinemia or hemoglobinuria. While there is no direct decomposition of hemoglobin or transformation of it or hematin to hematoporphyrin, there is every reason to believe that hemoglobin is its source.

Nor are the porphyrins likely to be formed in the intestinal canal, absorbed in the blood, and excreted in the urine. They must be due to endogenous formation in the body cells, but we do not know in which ones. It is natural to think of the liver as the place of formation, especially as pronounced disease of this organ has been demonstrated (as in our Cases 2 and 3). The frequent simultaneous appearance of urobilinuria supports this view, as it is considered a sign of hepatic insufficiency. This intimate association between the two substances was shown in our Case 4, in which urobilinuria followed hematoporphyrinuria. It has been thought that bilirubin may furnish material for hematoporphyrin (hydrobilirubin resembles urobilin and is isomeric with it), but we know nothing about it. Recently, the muscle pigment, myohemoglobin or myohematin, has been thought of as a source, but its genesis also is not clear. However, by the action of sulphuric acid, a porphyrin may be split off from it.

We are also in ignorance in regard to the toxic hematoporphyrinuria in poisoning with sulphonmethane, sulphonethylmethane and lead, but the genesis is probably the same as in the idiopathic form.

As has been stated before, a special disposition seems essential, a reduced mental and bodily vitality. Greatly increased breaking down of muscle substance may be a factor. As regards the pathogenesis, we may assume that the hematoporphyrins have a toxic action and produce degeneration in the nervous system and possibly also arteriosclerosis and chronic nephritis¹¹. This is supported by certain experimental data, but it is not by any means proved. It must in particular be remembered that the congenital form is not associated with actual toxic phenomena, but with a photosensibilization.

10 Fischer, Hans. Munchen med Wchnschr **70** 1143 (Sept 7) 1923

11 Snapper (Footnote 3) has recently claimed that the symptoms in this disease are produced by pressure on the retroperitoneal nerve plexuses (in one of his cases, by tuberculous glands, and in another by a hydronephrosis), resulting in hemorrhagic erosion of the stomach, intestinal colic, and an injurious influence on the liver, and formation of hematoporphyrin. This however, seems to me improbable as demonstrable abdominal lesions, which might have such injurious influence on the nervous system, are usually lacking.

CALCIUM TREATMENT FOR EDEMA *

REED ROCKWOOD, MD

AND

CHARLES W BARRIER, MD

ROCHESTER, MINN

Meyer and Cohn,¹ in 1911, studied the effect of various salts on the weight and mineral balance in normal infants. They found that by giving calcium salts they could cause a decrease in weight due to water loss. In the case of calcium chloride, they found that the calcium ion seemed to be largely excreted in the stool, while the chlorine ion was excreted in the urine in combination with other bases.

Schultz,² in 1918, reported ninety-three cases of war nephritis which he had observed and treated. On the basis of the work of Meyer and Cohn, he tried the effect of large doses of calcium chloride, and in many instances the edema disappeared completely. The calcium was not always effective, however. In certain of the resistant cases, there was apparently also a cardiac factor, and occasionally a combination of digitalis and calcium produced diuresis and loss of edema fluid.

Hulse,³ in 1920, reported eight cases of war nephritis with edema treated successfully by doses of calcium chloride of from 15 to 20 gm a day. He believed that the calcium in some manner freed the sodium chloride and water that were held by the tissue colloids. He emphasized the fact that, besides the reduction of the edema, renal function improved definitely.

Blum⁴ and his colleagues, in studying the action of various diuretics

* Work done in the Division of Medicine, Mayo Clinic

1 Meyer, L F, and Cohn, S Klinische Beobachtungen und Stoffwechsel Versuche über die Wirkung verschiedener Salze beim Saugling, Ztschr f Kinderh 2 360-419, 1911

2 Schultz, E Klinische Beobachtungen über Nierenentzündung bei Kriegsteilnehmern, Ztschr f klin Med 86 111-138, 1918

3 Hulse, W Ueber den Einfluss der Kalksalze auf Hydrops und Nephritis, Zentralbl f inn Med 41 441-454 (June 19) 1920

4 Blum, L Le traitement des affections inflammatoires des séreuses par le chlorure de calcium, Presse med 30 221-225 (March 15) 1922 Blum, L, Aubel, E, and Hausknecht, R L'action diurétique des sels de calcium dans les œdèmes généralisés Mecanisme de cette action, Bull et mem Soc med d hôp de Paris 45 1561-1569 (Nov 25) 1921, Action diurétique des sels de calcium Mecanisme de cette action, Compt rend Soc de Biol 85 950-952, 1921, Modification de la composition minérale du sang et des humeurs après ingestion de chlorure de calcium, Compt rend Soc de Biol 85 1159-1162, 1921, L'action diurétique des sels de calcium dans la néphrite avec œdèmes, Bull et mem Soc med d hôp de Paris 46 206-214 (Feb 3) 1922 Blum, L, Aubel, E, and Levy, R L'action diurétique des sels de potassium dans les épanchements ascitique et dans les œdèmes dits essentiels, Bull et mém Soc méd d hôp de Paris 45 1504-1513 (Nov 18) 1921 Blum, L, and Bang, O L'action diurétique des sels de calcium dans l'ascite de la cirrhose du foie, Bull et mém Soc med de hôp de Paris 45 1569-1572 (Nov 25) 1921 Blum, L, and Schwab, H L'action du chlorure de calcium dans les hydropsies cardiaques, Bull et mem Soc méd d hôp de Paris 46 214-220 (Feb 3) 1922

on edema, in 1921, found that large doses of potassium salts (10 gm a day) reduced edema. Fearing the toxicity of these salts, they turned to calcium, and found that they could substitute 10 gm a day of calcium chlorid with equal benefit. They secured very good results in causing a disappearance of the edema of nephritis and of the idiopathic edema of the nephrosis type. No benefit was obtained in cases of edema of cardiac origin, in fact, a few of the patients became worse. In ascites due to cirrhosis of the liver, and in pleurisy with effusion, the amount of fluid was diminished, or removed entirely in certain cases. Blum and his associates studied the electrolytes in the urine, and found that the calcium apparently caused increased excretion of sodium. When the sodium ion was retained, water was retained with it, when it was excreted, diuresis occurred. These observers also found that calcium did not produce good results unless the patient was on a diet that was also low in salt, and that giving both calcium and sodium chlorid produced little change. These conclusions have been confirmed in part by the work of Brelet⁵ and Krummenacher⁶.

Atchley, Loeb and Benedict⁷ studied the electrolytic partition in the blood and urine in a case of diabetic edema under treatment with calcium chlorid. They also found that the chlorin ion was largely excreted in the urine as the ammonium salt. The excretion of the sodium ion in the urine was markedly increased, while the excretion of the calcium and potassium ions was only moderately increased.

Haldane, Hill, and Luck⁸ tried the effect on the normal person of large doses of calcium chlorid taken by mouth. They found that there was marked increase in the output of ammonia in the urine, and believed that the bicarbonate ion was replaced by the chlorin ion in the blood and possibly also in the tissues, and that a mild acidosis resulted. They thought it possible that the increased acidity brings the proteins of the blood and tissues nearer their iso-electric point and releases the cations which are held in Donnan equilibrium, causing a fall in osmotic pressure and a consequent loss of water. This hypothesis will not explain results such as we have secured with calcium lactate. Bowler and Walters,⁹ in their experimental work on the intravenous injection of calcium chlorid, have also confirmed this marked diuretic action.

5 Brelet, M. L'action diurétique des sels de calcium, Gaz d hop **95** 905-906, 1922

6 Krummenacher. Le traitement de la pleuresie avec épanchement par le chlorure de calcium, Ann d med **13** 204-242 (March) 1923

7 Atchley, D W, Loeb, R F, and Benedict, E M. Physicochemical Studies of Calcium Chlorid Diuresis, J A M A **80** 1643-1644 (June 2) 1923

8 Haldane, J B S, Hill, R, and Luck, J M. Calcium Chloride Acidosis, J Physiol **57** 301-306 (June) 1923

9 Bowler, J P, and Walters, W. Clinical Results of Intravenous Injections of Calcium Chlorid, to be published

Fischer¹⁰ has emphasized the dehydrating action of various salts on the different tissue colloids of the body. Some of the results following administration of these large doses of calcium might possibly be interpreted in the light of his general theory of the dehydrating action of large amounts of salt.

We are here reporting seven cases of edema in which calcium was used. Our first observations were made in September, 1922. Because Bowler and Walters had found that administration of large doses of calcium intravenously resulted in toxic symptoms, we did not use the doses recommended in the literature, but much smaller ones, with not very satisfactory results. The results of Bowler and Walters apparently do not apply to large doses of calcium given by mouth. In April, 1923, we gave calcium in large doses for the first time, in a case of very resistant diabetic edema. The results were spectacular.

REPORT OF CASES

CASE 1—History—A man, aged 43, came to the Mayo Clinic, March 30, 1923, for treatment with insulin. He had had glycosuria for fourteen months with duodenal ulcer, for which a gastro-enterostomy had been performed at the clinic. He had been under dietary management for diabetes at the clinic, and had returned home. In the interim, he had become somewhat discouraged, and had not paid close attention to his diet. The details of his stay in the hospital may be noted in Chart 1 and Table 1.

Treatment and Course—The patient's weight rose from 129 to 187 pounds (58.6 to 85 kg.) in seventeen days. At the beginning of the second period (Chart 1), treatment with insulin was started, and the diet and insulin dosage were maintained with little change throughout his stay in the hospital. The urine was practically sugar free at all times. In the third and fourth period, an attempt was made to control edema by the Kariell diet, by a dry diet very low in salt, and by magnesium sulphate given three times a day. Instead of reducing in weight, he actually gained during this time. The urine output was persistently low. April 16, calcium lactate was started (6 gm a day). The first dose was given at noon. During the afternoon and evening a moderate diuresis appeared for the first time, and for this twenty-four hour period, the urinary output was more than twice that of any day in the preceding week. On the second day, the patient had a little diarrhea, and the urine output diminished, although the enormous doses of magnesium sulphate given previously had not caused this. During the fifth, sixth and seventh periods, the calcium lactate was gradually increased until the patient was receiving 12 gm a day. The urine output increased markedly, and the weight fell rapidly. In the eighth period, the calcium was stopped in order to determine positively whether the diuretic effect was due to the calcium. In this three-day period, the diuresis was checked, and the weight remained constant, while the nitrogen balance of the patient, for some unknown reason, became negative. Jansen¹¹ has shown in a metabolic study of famine edema, that most cases appear to have a negative nitrogen balance. With the exception of the three-day period, this was not true in this case. When administration of calcium was resumed in the ninth

10 Fischer, M. Oedema and Nephritis Ed 2 New York, John Wiley & Sons, 1915

11 Jansen, W H. Die Odemkrankheit, Deutsch Arch f klin Med 131· 144-200 (Feb) 330-370 (March) 1920

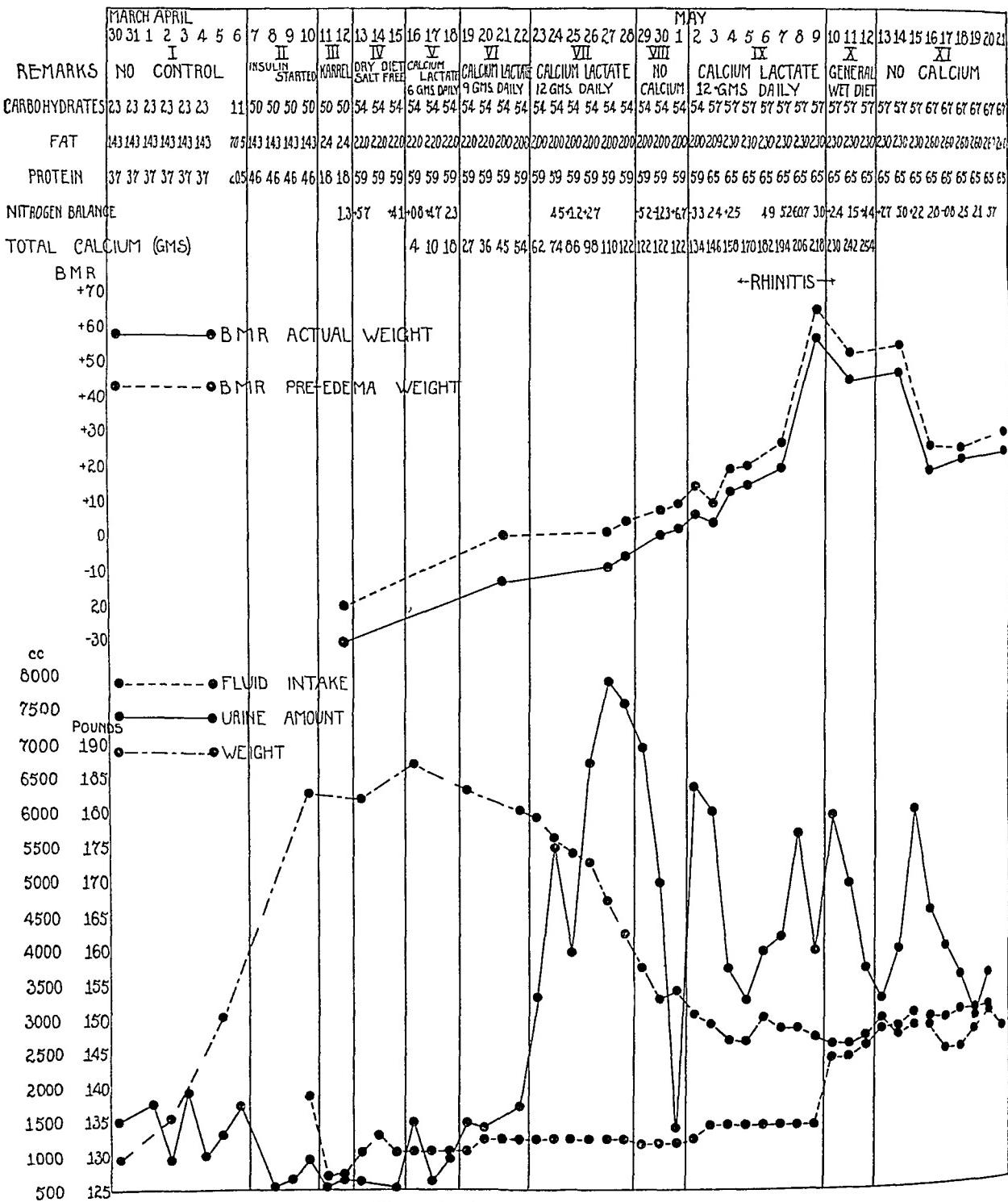


Chart 1—Findings in Case 1

period loss of weight and diuresis reappeared. In the tenth period, the patient was allowed his regular diet, which contained a great deal of water, and the calcium was also continued. In the eleventh period, the calcium was discontinued and the patient was kept under observation, but edema did not recur. He was dismissed from the clinic, May 21, and has not had a recurrence of edema for five months.

TABLE 1—Effect of Calcium in Diabetes Mellitus with Edema (Case 1, a Man, Aged 43, height, 5 Feet 9½ Inches)

Date	Weight, Pounds	Fluid Intake, Cc	Urine, Cc	Basal Metabolic Rate Calculated on		
				Preedema Weight	Actual Weight	
3/30/23	129 5		1,500			
4/ 1/23			1,750			
4/ 2/23	135 5		550			
4/ 3/23			1,950			
4/ 4/23			1,000			
4/ 5/23	130 5		1,300			
4/ 6/23			1,700			
4/ 8/23			750			
4/ 9/23			600			
4/10/23	183	1,800	900			
4/11/23		631	550			
4/12/23		631	600	-20		-32
4/13/23	182	1,076	775			
4/14/23		1,354				
4/15/23		1,160	500			
4/16/23	187	1,160	1,500			
4/17/23		1,160	600			
4/18/23		1,160	950			
4/19/23	183 5	1,160	1,500			
4/20/23		1,248	1,400			
4/21/23		1,248		0		-13
4/22/23	180	1,248	1,750			
4/23/23	179 5	1,248	3,300			
4/24/23	176	1,248	5,500			
4/25/23	174 5	1,218	4,000			
4/26/23	172 5	1,248	6,750			
4/27/23	167 5	1,214	7,900	0 + 4		-11 - 8
4/28/23	162 5	1,248	7,600	+ 3 + 4		-7 - 7
4/29/23	157 5	1,198	6,700			
4/30/23	153	1,198	5,000	+ 8 + 7		+ 1 0
5/ 1/23	154	1,198	1,400	+ 9 + 9		+ 2 + 2
5/ 2/23	151	1,232	6,350	+13 + 12		+ 5 + 6
5/ 3/23	149 5	1,419	6,000	+ 8 + 9		+ 2 + 3
5/ 4/23	147	1,449	3,700	+19 + 17		+13 + 10
5/ 5/23	147	1,449	3,300	+21 + 20		+15 + 14
5/ 6/23	151	1,449	4,000			
5/ 7/23	148	1,449	4,200	+28 + 23		+18 + 21
5/ 8/23	148	1,449	5,700			
5/ 9/23	147	1,449	4,000	+70 + 60		+61 + 52
5/10/23	146 5	2,407	5,900			
5/11/23	146	2,407	4,000	+51 + 55		+43 + 47
5/12/23	147	2,607	3,700			
5/13/23	150	2,801	3,300			
5/14/23	147	3,057	4,000	+73 + 78		+44 + 49
5/15/23	148	2,872	6,000			
5/16/23	148	2,872	4,000	+23 + 29		+16 + 21
5/17/23	145 5	2,872	4,000			
5/18/23	145	3,072	3,600	+25 + 27		+20 + 22
5/19/23	147 5	3,072	2,800			
5/20/23	150	3,072	3,600	+25 + 33		+19 + 27
5/21/23	147					

The figures for fluid intake (Table 1) may seem a little high, but this is because they were calculated to include the water in the food and the water of metabolism besides the actual fluid intake.

Studies on the Chemistry of the Blood—A few chemical studies were made (Table 2). There was no acidosis. The serum calcium was not increased by calcium treatment. These two readings are no indication, however, of what was going on during the period of the elevation of the metabolic rate, since they were taken prior to that time. A twenty-four hour electrolyte partition of the

blood and urine was made, but showed nothing of especial significance. Blood volume and concentration studies were also made (Table 3). During the height of the edema, the blood showed considerable concentration, and during the diuresis, a loss of solids with resulting dilution. This is in accordance with the findings of Brown and Rountree¹² in certain cases of edema.

Basal Metabolic Rate.—One of the interesting points in this case is the change in the basal metabolic rate that followed the administration of calcium (Table 1). There was a marked increase during the period of calcium administration. There were no symptoms of hyperthyroidism, such as tachycardia, during this

TABLE 2.—Blood Chemistry in Diabetic Edema Treated by Calcium Chlorid (Case 1)

Date	Sugar, Mg	Carbon Dioxid, per Cent	Urea, Mg	Uric Acid, Mg	Creat- inin, Mg	Cal- cium, Mg	Amino acid Chlorin, Mg	Sodium, Mg	Nitrogen, Mg
<i>Period of Rising Edema</i>									
3/29	229	56							
4/10						8.8			
4/11			55	1.5	2.0				
<i>Period of Falling Edema</i>									
4/21						8.9	222	3.6	
5/10	170	59							5.84
<i>Urinalysis, Twenty-Four Hour Specimen</i>									
4/20						Gm 0.25	Gm 3.4	Gm 5.3	

period, and the patient did not have goiter. The only suggestive features were an unusually good appetite and a slight tendency to night sweats. All readings, with the exception of the first two, were taken in duplicate, and as the technic was that of the usual routine in the Mayo Clinic, as described by Boothby and Sandiford, we have no reason to question their accuracy.

Discussion.—The cause of the consistent and marked rise in the basal metabolic rate toward the end of the period of calcium administration and as the edema was decreasing is unknown. Evidence possibly tending

TABLE 3.—Hydremia Study (Case 1)

Date	Plasma Volume		Blood Volume		Hemo- globin (Palmer), per Cent	Water in Whole Blood, per Cent	Water in Plasma per Cent
	Total, Cc	Cc per Kg *	Total, Cc	Cc per Kg †			
<i>Period of Rising Edema</i>							
4/10/23	3,600	43	6,000	72	132	78	93
<i>Period of Falling Edema</i>							
5/12/23	4,493	64	6,418	91	99	85	92.3

* Normal value, 50 cc per kg.

† Normal value, 85 cc per kg.

to indicate that the increased metabolism was not due to the administration of calcium lactate was obtained by one of us, who took, with negative results, 259 gm of calcium lactate over a two-week period at the rate of 18 gm a day, and during the last five days was on a nephritic salt-free diet which contained less than 1 gm of sodium chlorid (Table 4).

12 Brown, G. E., and Rountree, L. G.: Volume and Composition of the Blood in Edema, to be published.

It is noteworthy that in this experiment on the normal subject the calcium content of the blood serum did not increase, nor was there any alteration observed in the electrocardiogram taken at the end of the period. Because of the evidence obtained in this experiment of a failure of absorption, or at least of no increased concentration in the blood, it is of no value in excluding the possible effect on the basal metabolic rate of raising the calcium content of the blood.

TABLE 4—*Effect of Calcium on the Basal Metabolic Rate of a Normal Man (R.R., Aged 26, Height, 5 Feet 8½ Inches)*

Date	Weight, Pounds	Pulse Rate	Respir- atory Rate	Respir- atory Quotient	Basal Metabolic Rate	Total Lactate Given, Gm	Serum Calcium Mg
6/9/23	186½	70	15	0.82	-1	0	
		70	12	0.81	-6		
6/11/23	187½	79	14	0.82	+3	0	
		80	13	0.83	+1		10.2
6/15/23	187	69	15	0.88	-2	43	
		75	17	0.83	-2		
6/15/23	188½	74	17	0.82	-4	97	
		72	16	0.82	-5		
6/20/23	187½	78	16	0.81	+2	133	11.8
		83	16	0.81	+3		
6/25/23	186½	69	17	0.75	-4	223	
		75	10	0.70	-6		
6/27/23	185½	72	16	0.87	-1	250	10.9
		72	15	0.86	-2		

TABLE 5—*Effect of Calcium in a Case of Diabetes Mellitus with Edema (Case 2, a Man, Aged 32, Height 5 Feet 6½ Inches)*

I Period of Rising Edema	Date	Weight, Pounds	Fluid Intake, Cc	Urine Output, Cc	Basal Metabolic Rate Calculated on			Total Calcium, Gm
					Actual Weight	Preedema Weight	Total Weight	
	5/31/23	118		2,600				
	6/1/23			2,850				
	6/3/23			3,200				
	6/4/23	125		1,500				
	6/5/23			3,600				
	6/6/23			3,600				
	6/7/23	132.5		2,850				
	6/10/23			1,450				
	6/11/23	134.5		2,100				
	6/12/23	137	2,931	1,550	-1	-3	+2	+2
	6/13/23	137	3,271	2,500				
II Salt-free Dry Diet								
	6/14/23	137	1,172	1,550				
	6/15/23	136	1,372	1,400	-12	-14	-7	-9
	6/16/23	131	1,472	1,000				
III Calcium Lactate (18 gm daily)								
	6/17/23	134	1,572	1,700				18
	6/18/23	134	1,572	900				36
	6/19/23	134	1,572	1,100				54
	6/20/23	134	1,372	900				72
	6/21/23	132.5	1,472	700				90
	6/22/23	132.5	1,072	800				108

CASE 2—A man, aged 32, weighing 118 pounds (53.6 kg.), who had had diabetes for a year and a half, following admission to the hospital, May 31, 1923, attained a weight of 137 pounds (62.2 kg.) in about twelve days. The details of his stay in the hospital are shown in Table 5. During the second period (Table 5), he was given a dry salt-free diet, but did not lose appreciably. In the third period, he was started on 18 gm of calcium lactate daily, but this had no effect on his weight or urine output except for the gradual loss of a pound or two. In the fourth period, calcium chloride in the same dosage was given June 23,

because of trouble at home, he was forced to leave the hospital, although he still had edema. He took 18 gm of calcium chlorid for a week at home, and then wrote that the edema had almost entirely disappeared and his weight had been reduced to 127.5 pounds (58 kg). During his stay in the hospital, both the salt and the water intake was limited, and this regimen was continued, in part at least, at home.

Discussion.—Most of the observations on the effect of calcium on edema have been made with calcium chlorid. Blum discusses the relative advantages of calcium chlorid and calcium lactate. He believes that the chlorin ion is mainly excreted in the urine, and the calcium ion in the stool, so that more sodium will be driven from the body if the excess of chlorin is used, since the excretion of the chlorin ion by the kidney will carry sodium with it. In Atchley's case, considerable chlorid was excreted with ammonium, rather than with sodium, and this finding is confirmed in the work of Haldane, Hill and Luck. The acidosis caused by the large doses of chlorid given by these workers probably explains this discrepancy. Meyer and Cohn, in one experiment with calcium lactate, found an increase rather than a decrease in body weight.

Calcium chlorid is much more difficult to take than calcium lactate. Gastric distress, nausea, vomiting and diarrhea are not uncommon, although these can be avoided to some extent by giving the drug in capsule form. We believe, therefore, that calcium lactate should be tried first, and if this is not effective (as in two cases reported here), an attempt should be made to use the chlorid.

It must be remembered that in changing from the same dose of calcium lactate to calcium chlorid, the same amount of calcium is not being given. Because of the higher molecular weight, the percentage of calcium by weight in calcium lactate is 13 per cent, while it is about 27 per cent in the case of calcium chlorid (U S P). Thus, in substituting calcium chlorid, we are increasing the dosage of calcium as well as adding the effect of the chlorin ion. All investigators observe cases which, for no known cause, are refractory to any form of calcium treatment.¹³

CASE 3.—A man, aged 41, who had moderately severe diabetes and severe acidosis, showed a plasma carbon dioxid capacity of 28 per cent. He was placed on restricted diet and insulin, and the acidosis gradually disappeared. In the course of sixteen days, his weight rose from 129 to 157.5 pounds (58.6 to 71.6 kg), and there was considerable generalized edema visible (Chart 2). He

13 Since the foregoing was written, we have observed another patient with diabetes and edema. He was given 18 gm of calcium lactate each day for three days, during which time his weight rose from 135 pounds to 143 pounds (from 61.2 to 64.9 kg). Nine grams of calcium chlorid was substituted for five days, which would give approximately the same amount of calcium by weight daily as that in the lactate. Diuresis occurred promptly, and the patient's weight dropped from 143 to 129.5 pounds (61.2 to 58.5 kg), and all vesicle edema disappeared. There was no restriction of water and salt during this time.

was then given large doses of calcium without restriction of his intake of water and salt. Calcium lactate was used first, and then, to hasten the process, a change was made to the same dosage of calcium chloride. After fifteen days of calcium treatment, the visible edema had entirely subsided. The diet throughout consisted of carbohydrate, 40 gm., protein, 57 gm., and fat, 179 or 235 gm. About 40 units of insulin were used daily. The figures given for fluid intake in this case also include the water in the food, and the water of metabolism as well as the actual fluid intake.

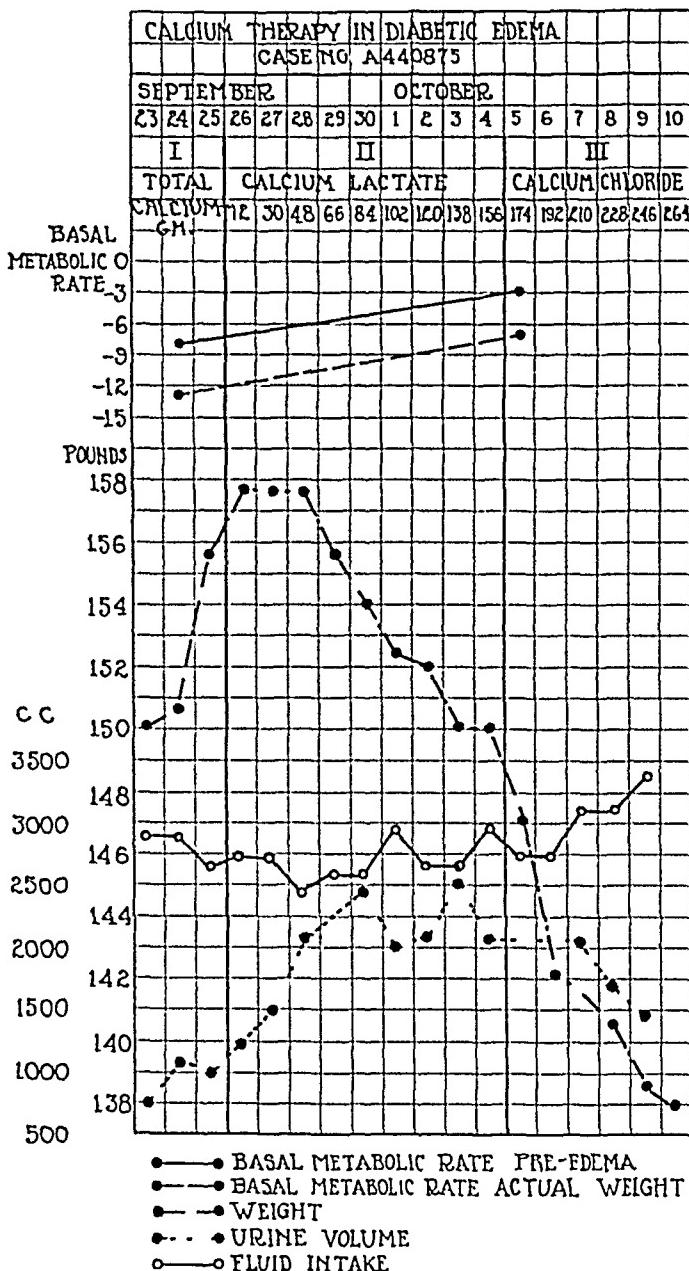


Chart 2—Findings in Case 3

Discussion—The French observers especially have called attention to the necessity for coincidental restriction of salt and water in order to secure results with calcium. In this case, we attempted to determine whether calcium would have a diuretic action without any salt and water restriction. It did have a definite diuretic effect. Doubtless, the

coincidental limitation of salt and water aids the action of calcium in reducing edema. In certain cases, such restriction alone is sufficient to clear up edema. Nevertheless, it is evident from this observation that the diuretic action of calcium and its therapeutic effect on edema is sometimes independent of salt and water restriction.

It will be noted that the final weight of this patient, 138 pounds (62.7 kg.), was considerably above the initial weight of 129 pounds, although there was no visible edema. This discrepancy, we believe, is due to two causes, one a true gain of fat and muscle, the result of dietary treatment and administration of insulin, which, from our experience in previous cases of this type, we believe might have been from 5 to 10 pounds (2.2 to 4.4 kg.) and the other, a correction of initial dehydration. The rise in the basal metabolic rate we believe to be due to the improvement in nutrition.

CASE 4—History—A man, aged 58, came to the Mayo Clinic, Aug 7, 1923, because of generalized edema and dyspnea.

Examination—Typical chronic glomerular nephritis was found, which, according to the history, dated back to an upper respiratory tract infection seven months before. There was albumin 3 in the urine and many casts. The phenolsulphonephthalein test showed a 30 per cent return. The blood urea was 37, the creatinin 2.3 and the uric acid 6.4 mg for each hundred cubic centimeters. The systolic blood pressure was 160, the diastolic 100.

Treatment and Course—The patient was placed on a diet of 40 gm of protein which was salt-free, with restriction of fluids to 800 cc., and 10 gm of calcium lactate in powder form was administered daily by mouth. The clinical course during the period of hospitalization is shown in Chart 3. Edema disappeared rapidly, and was absent for the first time in three months. The blood pressure became normal in eight days and remained so. In thirteen days, the blood uric acid went down to 3.6 mg, the urea to 2.4 mg, and the creatinin to 1.2 mg for each hundred cubic centimeters, while the urine showed only a trace of albumin and no casts. In fifteen days, the phenolsulphonephthalein output rose to 60 per cent. The effect of the calcium lactate seemed to wear away gradually, so that, by August 12 and 13, the diuresis was checked. As a result of administration of the same dose of calcium chloride, however, diuresis occurred again, persisting until the weight was down to normal.

Second Admission—The patient was well for two weeks after leaving the hospital. Then edema began to recur and gradually increased until he entered the hospital again, one month later, with a weight of 154 pounds (70 kg.). The administration of calcium chloride, 18 gm daily, was resumed, with restriction of salt and water. A marked diuresis again resulted, and the weight fell as much as 5 pounds (2.2 kg.) a day, reaching 118 pounds (53.6 kg.) the twenty-third day. On the second admission, the phenolsulphonephthalein output was 22 per cent. When the weight had returned to normal, it was 55 per cent.

Discussion—The improvement of renal function after the reduction of edema is of especial interest in this case. Hulse called attention to this in connection with his use of calcium in war nephritis. He ascribed it to a possible action of calcium on the sympathetic nervous system, causing a relaxation of vascular spasm. It would seem to us more

plausible that edema of the kidney, coincident with the general edema, interferes with renal function, and that on the disappearance of this renal swelling, improvement in function occurs such as may be noted after decapsulation of the kidney, or in recovery from cardiac decompensation. In this case also, the advantage of calcium chloride over the same dose of calcium lactate is evident from the fact that after the influence of the calcium lactate was no longer apparent, calcium chloride was still effective.

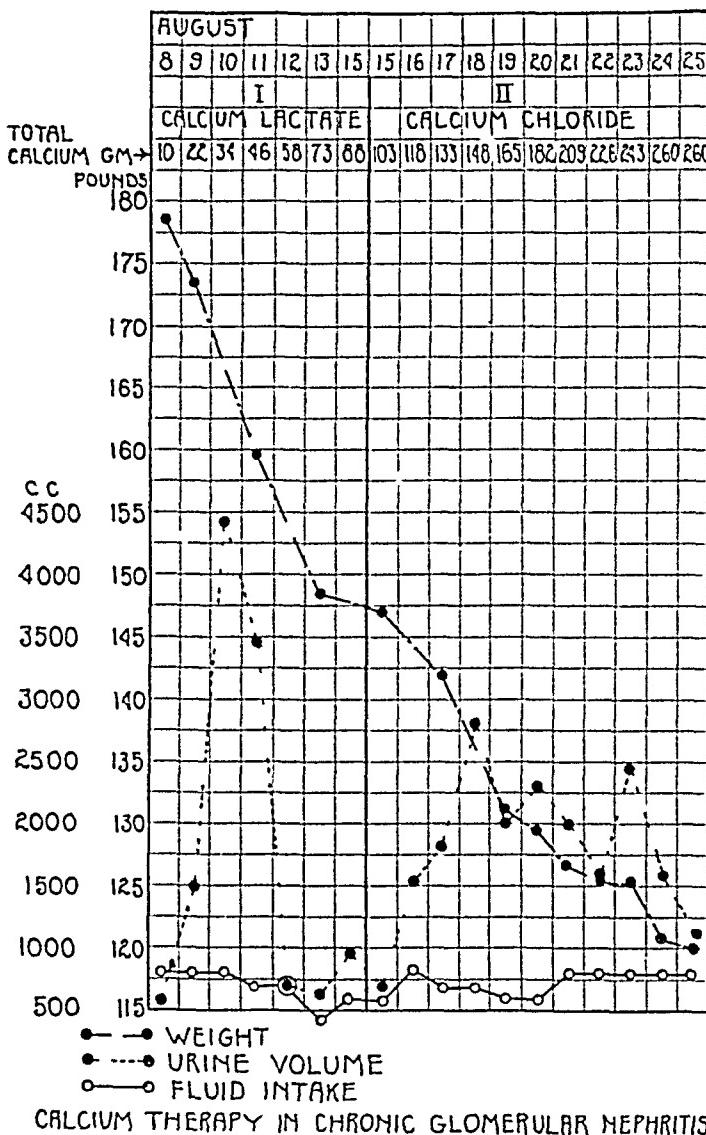


Chart 3—Findings in Case 4

CASE 5—A man, aged 37, came to the clinic with nephrosis and edema, which had been present intermittently for eighteen months, and continuously for two months. In spite of the administration of 18 gm of calcium lactate for six days, and 18 gm of calcium chloride daily for six days more, there was no diuresis, although there was a gradual decline in weight from 188 to 167 pounds (85.4 to 76 kg.) in eighteen days. The salt and water intake were limited throughout the entire period, and frequent hot packs and sweats were given.

Discussion—In this case, we cannot say that the calcium had any effect. The restriction of salt and water may have been responsible for the loss of weight. On the other hand, the hot packs and sweating may have obscured a tendency to a rise in urine output due to the calcium.

CASE 6.—A youth, aged 19, came to the hospital because of nephritis which he had had since childhood, but more particularly because of generalized edema of one month's duration. He had chronic glomerular nephritis and general edema and was kept in the hospital for twenty-eight days (Chart 4). Salt was

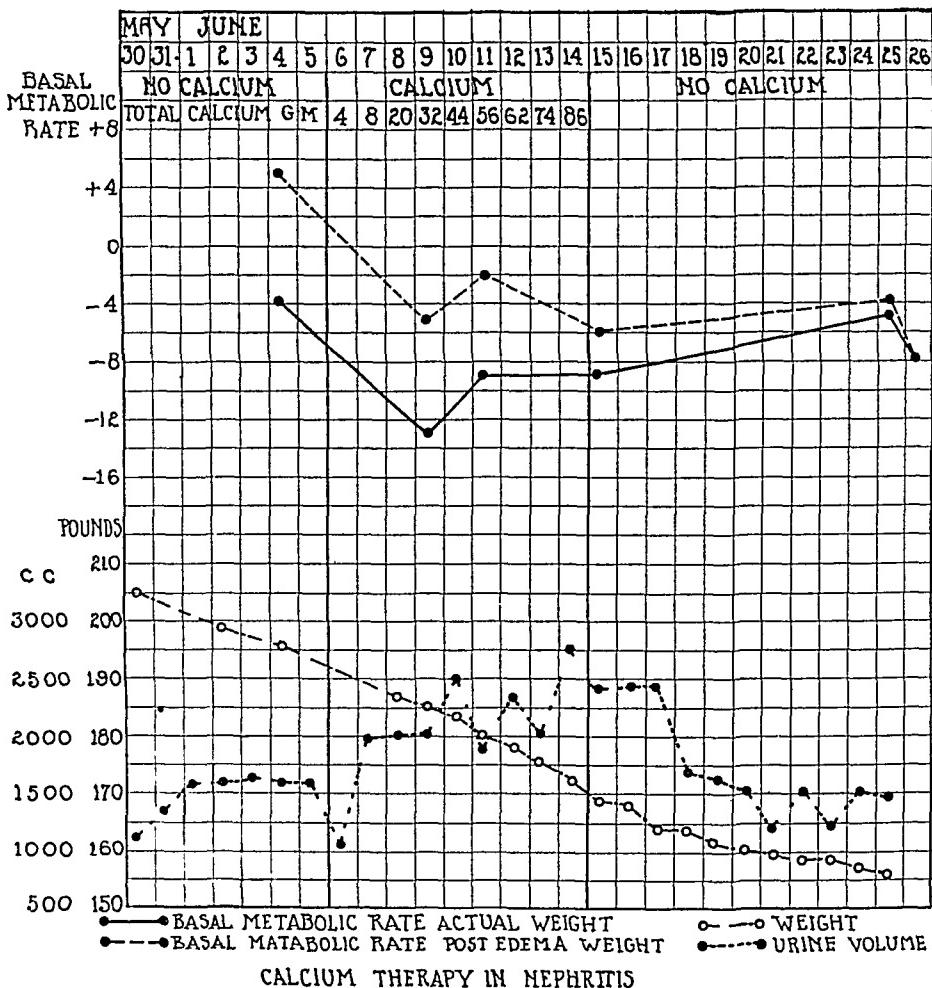


Chart 4.—Findings in Case 6

restricted, and the daily fluid intake was limited to 800 cc throughout. Calcium lactate was also used, and the edema subsided completely. This patient returned to the hospital in three months with a rather marked nitrogen retention, which had not been present before. Despite this evidence of progressive nephritis, edema had not recurred.

Discussion—In this case, we do not feel convinced that the drop in weight was due to the calcium alone, since this had started before calcium was tried. However, the diuretic effect of the calcium was marked.

(Chart 4) The edema was lost without any significant variation in the basal metabolic rate

CASE 7—History—A man, aged 35, entered the clinic, May 21, 1923, because of edema, which he had had for about three months. His renal function, except for poor excretion of water and salt, was good, and a diagnosis of nephritis of the nephrosis type was made.

Treatment and Course—The patient was kept on a low fluid intake for seven days with but 4 pounds (1.8 kg) loss in weight, and with no diuresis or noticeable change in edema. He was then put on calcium lactate, 18 gm a day, for

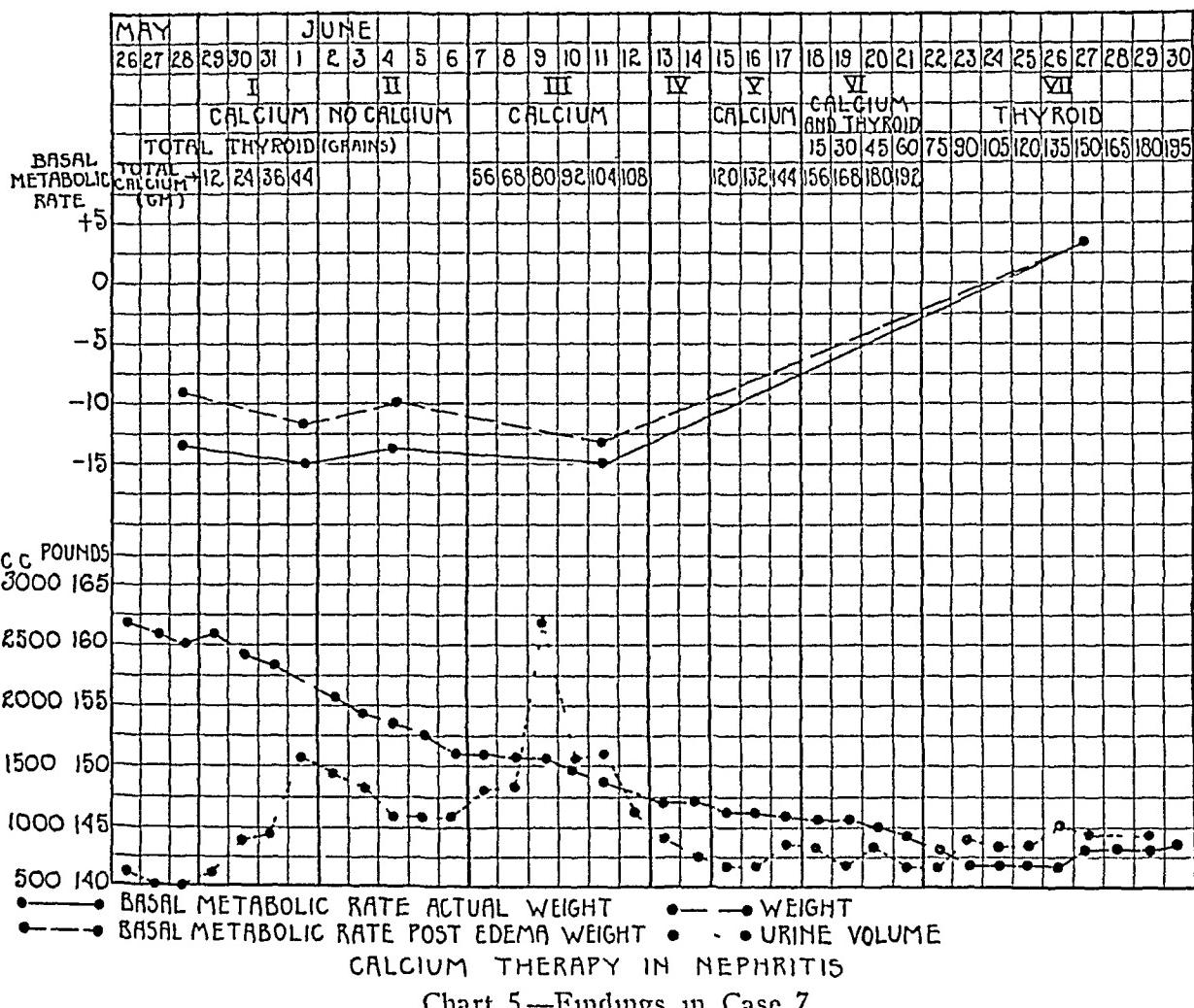


Chart 5—Findings in Case 7

periods of four days, with intervals between in which calcium was not given. In each period in which calcium was given, there was diuresis with loss of edema fluid, which stopped when the administration of calcium was discontinued. In thirty-one days, there was a loss of 20 pounds (9 kg). The total dosage of calcium was 188 gm. The administration of thyroid extract in the sixth and seventh periods, while causing an elevation of the basal metabolic rate, did not increase the loss of water.

After the patient left the hospital, he was free from edema for a month. It then recurred slightly, following a cold and diarrhea. He was on a salt-free diet throughout, but this seemed to have no influence on his condition. He returned to the clinic in October, 1923, with a trace of edema about his ankles, and weighing 148.5 pounds (67.5 kg). The edema was again controlled with calcium

GENERAL COMMENT

Denis and Minot¹⁴ and others have shown that the upper limit of serum calcium tends to be fixed, and that it seems to be impossible to raise it for any length of time in spite of the ingestion or injection of large amounts of calcium. This was true also in some of our cases. Our doses of calcium have been larger and were given over longer periods of time than any we can find in the literature in cases in which the serum calcium was also determined.

A summary of these data appears in Table 6.

Recent analyses show that milk contains from 0.99 gm to 1.6 gm of calcium for each liter, corresponding to from 7 to 12 gm of calcium lactate for each liter. This makes average milk the equivalent of a 1 per cent solution of calcium lactate. Milk has long been highly valued

TABLE 6.—The Effect of Treatment with Calcium on the Serum Calcium

Case	Diagnosis	Date	Total Calcium Salts Administered, Gm	Total Calcium (Calculated) Gm	Serum Calcium (Kramer Tisdall) Mg for Each 100 Cc
Normal		6/11/23	0	0	10.2
		6/20/23	133	17.2	11.8
		6/27/23	259	33.6	10.9
3	Diabetes	9/24/23	0	0	8.4
		10/8/23	228	39.6	9.3
1	Diabetes	4/10/23	0	0	8.8
		4/21/23	45	5.8	8.9
2	Diabetes	6/14/23	0	0	9.8
		6/20/23	72	9.3	10.5
6	Nephritis	6/1/23	0	0	9.0
		6/14/23	86	11.1	9.4
5	Nephrosis	10/4/23	0	0	10.7
		10/17/23	216	43.2	9.1
7	Nephrosis	5/25/23	0	0	9.2
		6/4/23	44	5.7	10.5
		6/14/23	108	14.0	9.7

in the treatment of acute nephritis. It has been used on more or less empiric grounds, and from the high protein and water content does not appear to be an ideal food when renal function is impaired. In the usual "milk cures," it is given in an amount of from 1 to 2 liters daily, and the calories in such amounts are insufficient to maintain nutrition, even with the patient in bed. The protein is from 30 to 40 gm for each liter, which makes a diet consisting of two liters of milk rather richer in protein than is desirable in cases of nephritis with nitrogen retention, and salts other than calcium are present in not inconsiderable quantities. Some of the favorable effects ascribed to a milk diet in the past in such cases may therefore be due to the diuretic effect of the high calcium content. Bastedo¹⁵ quotes Raphael, who studied the diuretic action of

14 Denis, W., and Minot, A. S. Effects of Feeding with Calcium Salts on the Calcium Content of the Blood, *J. Biol. Chem.* **41**: 357-361 (March) 1920.

15 Bastedo, W. A. *Materia Medica, Pharmacology, Therapeutics, Prescription Writing for Students and Practitioners*, Philadelphia, W. B. Saunders Company, 1915.

various fluids and found that a liter of water caused a 100 per cent increase in the urine output, while a liter of milk caused an increase of 153 per cent. If calcium is the cause of the beneficial action of milk diets in nephritis it would seem logical to prescribe diets in which the protein, salt, fluid and caloric value have been properly adjusted, and then to give the necessary amount of calcium in addition, rather than to employ milk alone. It is possible that calcium in the combinations in which it is present in milk may be absorbed at a different rate than when it is given as the pure salt.

SUMMARY

We have tried the effect of large doses of calcium salts (from 12 to 18 gm daily) in cases of massive edema of diabetic and nephritic origin. In six of seven cases, most of which had been resistant to other methods of treatment edema disappeared completely. In one case, edema disappeared, but the part played by the calcium is questionable. In two cases of nephritis, edema recurred later. None of these cases were complicated by significant myocardial damage, and in none was any other diuretic given with the calcium. In the few instances in which we used small doses of calcium (from 1 to 3 gm daily), little or no effect was observed. In some of the cases edema was reduced by calcium lactate. In other cases calcium chlorid seemed more effective. Large doses of calcium do not seem to increase the amount of serum calcium. In one case of chronic glomerular nephritis, renal function was definitely improved as the edema subsided. In one case of diabetic edema, the basal metabolic rate rose during the administration of calcium from —13, April 21, to an average of +57, May 9. A similar dose of calcium did not produce a change in the basal metabolic rate of a normal person. In the other cases of edema discussed, the administration of calcium had no effect on the basal metabolic rate. The high calcium content of milk may explain its diuretic action, and thus its popularity in the treatment of acute nephritis.

Book Reviews

BLOOD CHEMISTRY COLORIMETRIC METHODS By WILLARD J STONE
Price, \$2 25 Pp 71 New York Paul B Hoeber, 1923

The author publishes in this book the methods of blood analysis devised by Folin and Wu, Benedict, Van Slyke, Myers, Bloor and others To these are added instructions for conducting certain renal function tests with clinical comments on renal function Brief dietary suggestions regarding the treatment of nephritis and diabetes complete the text No claim of originality is made for any of the tests described, nor does the text carry with it a conviction that the author offers more than a compilation of certain laboratory tests which, in many other laboratory texts, are more comprehensively presented, or are described equally well as part of a general laboratory manual

LECTURES ON ENDOCRINOLOGY By WALTER TIMME, M D, Attending Neurologist, Neurological Institute, New York, Professor of Endocrinology, Broad Street Hospital, Professor of Nervous and Mental Diseases, Poly-clinic Medical School and Hospital Price, \$1 50 Pp 123, with 27 illustrations New York Paul B Hoeber, 1923

This monograph is a reprint of an article published under the title of "Clinical Endocrinology" in 1921 It contains brief chapters on the thymus, pineal glands, the thyroids, the suprarenals, the pituitary, and the gonads The pancreas and the parathyroid glands are not discussed The treatment of this subject is clinical and the neurologic aspects of the several alleged endocrine syndromes are stressed The author accepts, without much critical discussion many of the theories of pluri-glandular syndromes and mutual endocrine interaction This may be necessary in such a brief paper, but may mislead a reader who accepts the book as a reliable authority There is little evidence that the pineal body is an endocrine organ, and this applies to the thymus gland also

The author assumes as a demonstrated fact a depression of thyroid activity by gonad hormones "A good example of such hyperthyroidism is that seen in some women after the menopause—the ovarian function having ceased, the thyroid is left without sufficient counterbalance, and a hyperthyroid state ensues This awakens over-activity of the adrenals with resulting high blood pressure" It is certain that spaying in animals below man produces no symptoms indicating hyperactivity of the thyroid, and neurocirculatory disturbances of the menopause have not yet been shown to be due to excessive thyroid secretion The volume contains many such plausible statements that are not based on demonstrated facts For instance—"During the period following menstruation there is usually a diminished thyroid activity"

The author promises an elaboration of the present theme in the near future If, when this is done, he should combine his pleasing and easy style with greater critical discernment, he would do a distinct service to medical science in this difficult field

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A STUDY OF MIXED LEUKEMIA WITH THE REPORT OF A CASE¹

RUDOLPH C LOGEFEIL, MD
MINNEAPOLIS

So-called mixed leukemia, that is, a combination of myelogenous and lymphatic leukemia occurring in one person at the same time, is such a rare condition that I have felt it worth while to report this case, as well as enter into the problem which a study of the case presents and to review the literature on previously reported cases.

Turk¹ was the first to report a case of so-called mixed leukemia. This was in 1906, before the congress of Internal Medicine. He reported four cases at this time which he considered to be mixed leukemia. He apparently was the first to appreciate, at least, to publish the fact that an activity of the lymphatic and myeloid systems could go on in an individual at the same time. In the same year, Hirschfeld reported a case which he called true mixed leukemia, and in 1909, Herz² reported a case which he felt he could call by no other name. In 1913, Herxheimer³ discussed the question of mixed leukemia and reported a case which he believed to be a true example. Since this time there have been various cases of so-called atypical leukemia reported, some of which may be in the classification bearing the foregoing title, but the authors have not labeled them as such.

In arriving at the diagnosis of mixed leukemia in any case, many points of discussion arise which entail opinions and theories which are vital issues among hematologists of the present day. Many prominent hematologists such as Meyer and Heineke,⁴ Fabian,⁵ Naegeli,⁶ and

* From the Hematological Laboratory, Department of Animal Biology, University of Minnesota.

¹ Turk, W. Berichte aus den Wissenschaftlichen Vereinen, Wien med Wehnschr **54** 1430, 1904, ibid, Ueber Regeneration des Blutes unter normalen und krankhaften Verhältnissen, Zentralbl f allg Path u path Anat **19** 895, 1908.

² Hirschfeld, H. Ueber Leukämie, Folia haematol **3** 332, 1906, ibid, Weiteres zur Kenntniss der myeloïden Umwandlung, Berl klin Wehnschr **43** 1064, 1906.

³ Herz, A. Zur Frage der gemischten Leukämie, Wien klin Wehnschr **22** 1030, 1909.

⁴ Herxheimer, G. Ueber einen combinierten Fall von lymphatischer und Myeloblastenleukämie, Zentralbl f allg Path u path Anat **24** 897, 1913.

⁵ Meyer, E., and Heineke, A. Ueber Blutbildung bei schweren Anamien und Leukämien, Arch f klin Med **88** 435, 1907.

⁶ Fabian, E., Naegeli, O., and Schatzloff, P. Beiträge zur Kenntniss der Leukämie, Virchows Arch f path Anat **190** 473, 1907.

⁷ Naegeli, O. Blutkrankheiten und Blutdiagnostik, Edition 3, Leipzig, 1919, Ver Wiss Verleger.

Schatloff⁶ deny the possibility of the existence of a mixed leukemia, while other equally prominent men such as Herz,³ Hirschfeld,² von Domarus,⁸ Herxheimer⁴ and Downey feel that they cannot explain the findings in these cases except on the basis of a true mixed leukemia Dohrer, Pappenheim⁹ and others take an intermediate position, while many do not express their opinion on the subject at all

While studying this case, certain observations gave information and suggested opinions on the old but still acute question among hematologists, namely, the theory of the origin of blood cells. This will be discussed briefly at a later time.

Before calling a condition mixed leukemia, Browning demands proof that the myeloid and lymphatic tissue of the body must be stimulated simultaneously in the same way and in the same place, with evidence in the form of active myeloid and lymphatic metaplasia. According to this definition, I feel that the following case which I shall report must be called a mixed leukemia. I cannot see how the findings in the blood smears and histologic structures of the tissues can be explained on any other basis.

The condition occurred in a patient of Dr F W Schultz, of this city, who kindly allowed me to study and report it and who gave me the following records of the case.

REPORT OF CASE

History—R M W, a girl, aged 3 years, was brought to the physician for examination on Sept 6, 1921. She was the third child of a moderate sized family, the other children and parents were living and well. She was a full term infant, of normal birth and breast fed. She had measles and whooping cough but no recent illnesses. For two weeks before examination she complained of pain in the abdomen, arms and legs. The temperature had risen in the afternoons and the patient complained of being tired and of having a poor appetite. She did not sleep well. The bowels were regular but the patient had been losing weight.

Physical Examination—A fairly well nourished child was seen, with clear skin, firm muscular tone, normal glands, well-formed head with the fontanelles closed. The throat showed some inflammation. The chest formation was good. The lungs were clear throughout. The heart was normal in area and sound. The abdomen was normal. The liver and spleen were not felt. The rectum and genitals were normal. The extremities were symmetrical, with no enlargements. The reflexes were not exaggerated.

Urine examination was negative. Blood examination showed a hemoglobin of 65 per cent, red blood cells, 4,504,000, white blood cells, 11,400, differential polymorphonuclears, 45 per cent, lymphocytes, 50 per cent, mononuclears 3 per cent, transitionals, 1 per cent, eosinophils, 1 per cent. The Wassermann reaction was negative. The Pirquet test was negative. Another urinalysis on September 9 was also negative.

8 von Domarus. Der gegenwärtige Stand der Leukämiefrage, *Folia Haematol* **6** 337, 1908

9 Dohrer and Pappenheim. Ein weiterer Fall von akuter Microlymphoidozytenleukämie, *Folia Haematol* **16** 143, 1913

The patient returned, September 17, at which time she weighed 31 pounds, 5 ounces (14.3 kg) showing a loss of only 3 ounces (85 gm) since the first visit on September 6. The coagulation time of the blood was four minutes. Urinalysis was normal. Physical examination showed a slight puffiness over the left eye. No definite tremor was palpable. The patient complained of difficulty in walking, some malaise and being always tired. She walked with some difficulty. The swelling over the left eye was becoming more pronounced. The abdomen was normal, and there was no enlargement of the spleen or lymph glands determined at this visit.

On September 17 a tonsillectomy was done. The child did not seem to make a normal recovery from this slight operation, but remained weak and continued to run a fever.

A week later there was extreme prostration, pallor, malaise and drowsiness. The spleen was enlarged to 4 inches (10 cm) below the rib margin. There was no icterus and no general enlargement of the glands. The patient was sent to the hospital. It was at this time that acute leukemia was first suspected and the following and subsequent blood examinations confirmed the diagnosis.

On September 26 examination of feces (two specimens) showed microscopic blood present but no pus cells. A differential count was made at this time and the blood smear examined by Dr E L Gardner. His report read as follows: "Five hundred cells were counted with the following results: polymorphonuclears 6 per cent, lymphocytes, 15 per cent, transitionals, 1 per cent, promyelocytes and so-called stem cells, 45.25 per cent, myelocytes (neutrophilic) 55 per cent, basophilic, 0.3 per cent, eosinophilic, 0.3 per cent. Many nucleated red cells were noted with quite a few degenerating leukocytes, some having the nuclei extruded. There were practically no normal cells seen. All showed signs of marked bone marrow stimulation. The red blood cells were irregular and pale with some polychromatophilia. Lymphocytes were very hard to differentiate from the small promyelocytes." A blood examination had also been made on September 24. At that time the hemoglobin was 38 per cent, white blood cells 97,000 red blood cells, 2,140,000. Differentials showed polymorphonuclears, 6.75 per cent, lymphocytes, 92.75 per cent, large mononuclears, none, transitionals, 0.5 per cent. Dr Gardner noted that "there were some basophilic and neutrophilic myelocytes present, some poikilocytosis and polychromatophilia. There was uneven distribution of pigment in the red cells, some heavily stained others very pale. Four nucleated red cells were seen. No basophilic stippling." (The first differential count was made by Dr Schultz' laboratory technician. The last two smears were the only ones which were available to me for study, the others having been destroyed. The report of my study of these blood smears will be given later.)

Death occurred Sept 30, 1921. There were no important clinical changes during the last week of life.

The following is a copy of the necropsy, which was made by Dr E T Bell, professor of pathology at the University of Minnesota. The heart showed petechial hemorrhages in subepicardial tissue. The spleen was enlarged greatly, and weighed 300 gm. There were no adhesions. The various surfaces were well defined. The capsule was smooth and clear. The cut surface was pale with reddish mottling. No definite corpuscles were visible. There was a small accessory spleen about 1 cm in diameter in the great omentum, the cut surface had the same appearance. The liver weighed 690 gm. The capsule was smooth with yellowish mottling underneath. The cut surface was pale and mottled with regular yellowish spots about from 1 to 2 mm in diameter. The gallbladder was normal. The abdomen and intestines showed numerous petechial hemorrhages on serosa of the intestinal coils. There was a partial intussusception in part of the ascending colon in which the ileum was invaginated into the cecum and ascending colon. At the head of the intussusception was a large polyoid mass. The gastric juice was of a reddish-brown color suggesting the presence of blood. There were no changes in the small intestines. The intussusception

was evidently agonal. On opening this portion of the intestines, a polypoid mass was found at the head of the invaginated portion and attached to the wall of the cecum near ileocecal valve. The mass measured 4 by 3.5 by 1.5 cm. There was a central ulcerated area 3 cm wide. The mesenteric and preaortic lymph nodes were enlarged. The largest was 5 by 3 by 2.5 cm. The next largest was 2 by 2 by 2 cm. A number of small lymph nodes showed no change. In the base of the mesentery, the enlarged nodes were crowded closely together, forming a large tumor mass which was evidently the mass palpated through the abdominal wall. There were no other enlarged lymph nodes. The pancreas and adrenals were normal. The kidneys weighed 55 gm each, and were pale and cloudy. There was a small tumor mass in each, palpable and visible after capsule was removed. The bladder was normal. The ovaries were greatly enlarged. The thymus was not enlarged. The brain was normal, with numerous small infiltrated areas in the dura mater which eroded the underlying bone.

Microscopic Examination.—The large lymph nodes of the mesentery showed leukemic infiltration, necrosis and hemorrhage. The small mesenteric nodes showed leukemic infiltration. The polypoid mass in the cecum showed leukemic infiltration of the mucosa. The liver showed portal leukemic infiltration. The spleen showed leukemia infiltration of a large portion of the pulp, the corpuscles were indistinct. The kidney showed small nodules composed of lymphocytes. There were albumin casts in the lumina of the tubules. The pancreas showed small areas of lymphocytes. The diagnosis was acute myeloid leukemia.

MICROSCOPIC STUDIES

The blood smears were sent to Dr Hal Downey who, on examining them, immediately perceived that there was something unusual about the case. He saw in the blood smears all stages of developing myeloid and lymphoid cells, and it was at his suggestion and under his supervision that I have made an intensive study of this case.

Material and Staining.—Sections of the following tissues were available for examination. Polypoid mass in cecum, an enlarged mesenteric lymph node, spleen, liver, lung and kidney. They were all fixed in formaldehyde and stained according to the method of Dominici.

Only two blood smears were available for examination, as mentioned before. Ordinary Wright's stain was used in preparing them.

Intestinal Polypoid Mass Found in the Cecum.—Sections through this mass showed it to be due to an infiltration of leukemic cells into the mucosa. Most of the cells present were lymphocytes, although there were a few myelocytes and adult eosinophils seen. Necrosis was quite marked, especially in the small cells.

Lymph Nodes.—Sections through various portions differed somewhat, but I shall describe only two of the more typical areas.

1. In this area there were no definite follicles, but there was a general increase in the lymphatic tissue, which was spread out diffusely over the entire section. There were some areas suggesting follicles which had atrophied, with marked evidence of necrosis. The reticular tissue on the whole was filled with lymphocytes in various stages of development. No myelocytes were seen in the interfollicular or medul-

lary tissue, but some of the large blood vessels contained a few. In some areas the lymphocytes were more condensed and here mitosis was common.

2 The other most typical area showed a relative increase of the interfollicular tissue or pulp over that found in the foregoing area described. Atrophy of the follicles was more marked. The dying follicles showed marked necrosis of cells with no evidence of mitosis. Mitotic figures in the lymphocytes were not so much in evidence in this section. The lymphatic tissue was as a whole, a little more dense and concentrated. The interfollicular tissue showed many myelocytes mostly of the eosinophilic type. They were scattered diffusely in the reticular tissue of the medulla with no special relation to the blood vessels. In general there could be no definite distinction made between the cortex and medulla or the cells in these areas. The predominating cell was the medium sized lymphocyte although some small and large lymphocytes were present. Many of the myelocytes show small dark-stained nuclei, rich in chromatin, which were indistinguishable from the nuclei of many of the adjacent lymphocytes. Most of the lymphocytes present were of the typical adult type but there were some young lymphocytes scattered here and there among the former (Fig. 1).

Lung.—The various sections were about the same. There was no evidence of lymphoid follicle formation. The connective tissue of the alveolar walls contained many large typical eosinophilic myelocytes and some with smaller fine red granules, undoubtedly neutrophilic myelocytes. There were some other cells present in the reticular tissue which had a dark, purple staining, slightly irregular nucleus which was about the same size as those found in the myelocytes, but the chromatin was more dense and in irregular masses. The protoplasm took a basic stain and formed in a narrow ring about the nucleus. They were undoubtedly early or young lymphocytes. Also many cells were seen with dark, pyknotic, round nuclei showing more cytoplasm taking the basic stain. They were undoubtedly adult lymphocytes. Many of these cells could be seen undergoing mitosis. Adult eosinophils were also seen in the reticular tissue. Some of the alveoli were filled with blood and showed cells similar to those found in the blood smears. Large phagocytic cells were also seen.

In general, we found here a myeloid and lymphatic reaction or activity in the reticular tissue, with the former predominating slightly. Local development of myelocytes and lymphocytes was in evidence.

Kidney.—A typical section showed areas of marked leukemic cell infiltration, with atrophy of tubules and glomeruli, and many necrotic cells present. The infiltration was diffuse with no evidence of follicular arrangement. The great majority of the leukemic cells were lympho-

cytes, small, large and medium in size, with the latter predominating. There were some immature ones among them. An occasional lymphocyte showed mitosis.

There were cells which were a little larger than the adult lymphocyte, which had only a small ring of cytoplasm about a large nucleus which was very poor in chromatin, and had a very fine nuclear membrane. The nucleus was pale in appearance with only here and there a fine dot or strand of chromatin visible. I interpret this type as being the most immature cell present, it corresponds to the description of the "stem" cell as seen in the tissue. There were other cells, mixed in with

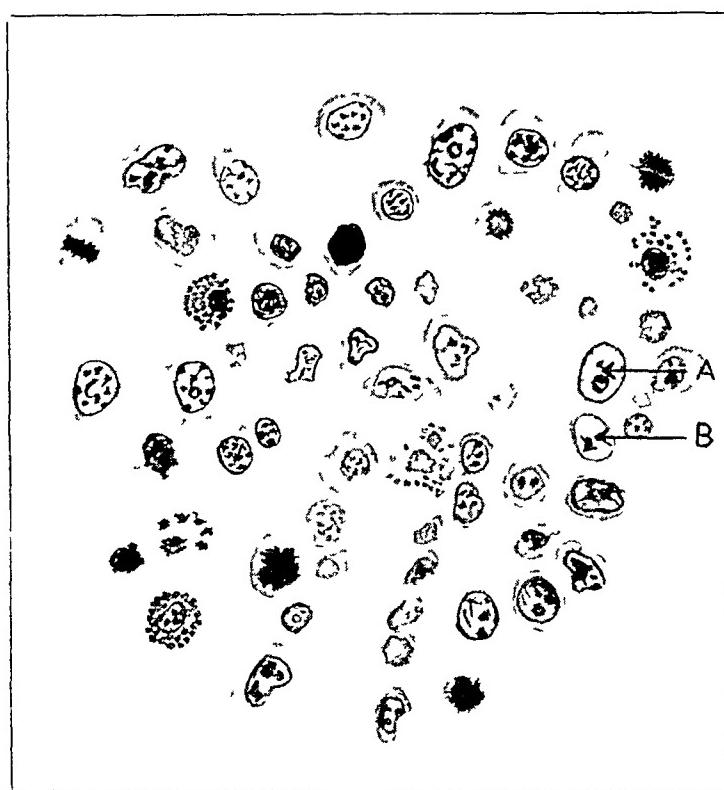


Fig 1.—A typical area in one of the enlarged mesenteric lymph nodes. Stem cell (*b*), immature lymphocyte (*a*), eosinophilic myelocytes, cells undergoing mitosis and degenerating cells are mixed together. Below cells *a* and *b* are three maturing lymphocytes, more mature than cell *a*.

these, showing just a little heavier nuclear membrane and just a little more chromatin within the nucleus, which I interpret as being somewhat more matured. Representative cells of succeeding stages in the differentiation of these lymphocytes to a typical adult lymphocyte were seen.

Scattered about between these developing lymphocytes were many neutrophilic and eosinophilic myelocytes. They were found in the tissues between the tubules, away from the blood vessels, and an occasional adult eosinophil or neutrophil was also seen. In these same areas

there were many cells with small, dark staining nuclei resembling the small lymphocyte in the tissue but having eosinophilic granules in the cytoplasm. Some of the granules were very young as was evidenced by the basophilic staining reaction.

There were also a few red blood cells scattered about in the tissues but no areas of hemorrhage. In the areas undergoing necrosis the leukemic cells as well as the kidney structures were affected (Figs 2 and 3).



Fig 2.—A low power view of the kidney, showing the nature of the leukemic cell infiltration. Note the atrophy of kidney structure.

Pancreas.—A typical section showed several small areas where pancreatic cells were undergoing atrophy and necrosis with replacement by connective tissue. There was infiltration of the leukemic cells in the connective tissue between the lobules, but no evidence of follicular arrangement. These areas showed a mixture of interesting cells. There were many eosinophilic myelocytes and neutrophilic myelocytes as well as mature cells. These eosinophilic myelocytes were of all sizes,

from that of typical eosinophil to that of the smallest lymphocyte. Many of them had a single small nucleus darkly stained and very rich in chromatin, very similar to those seen in lymphocytes in that same area. Occasionally two such cells, that is, an eosinophilic myelocyte and a lymphocyte could be seen side by side with the nuclei apparently identical. Some of the myelocytes as well as the lymphocytes had pyknotic nuclei and seemed to be degenerating. In these same areas, mixed in



Fig 3.—This is a higher magnification of a small area in Figure 2 marked thus □. The types of cells present and some of their characteristic features can be seen. Cells *a* and *b* are eosinophilic myelocytes. Cell *c* is an immature lymphocyte.

with the myelocytes, were many lymphocytes in various stages of development. The so-called "stem" cell as it appears in the tissue was also seen here and had the same characteristics as given in the description of these same cells found in the kidney. Many immature lymphocytes were seen. These young or early lymphocytes were very poor in chromatin with a thin nuclear membrane, and here, even more so than

in the kidneys showed definite nucleoli some only one while others had even two or three. Here as elsewhere the medium size lymphocyte was the predominating cell.

In a few places the leukemic cells had infiltrated between the acini near the edge of the lobule but on the whole the leukemic infiltration was limited to the interacinar connective tissue spaces. These were apparently widened in some places and occasionally showed small areas of hemorrhage. The blood vessels of the pancreas were filled with

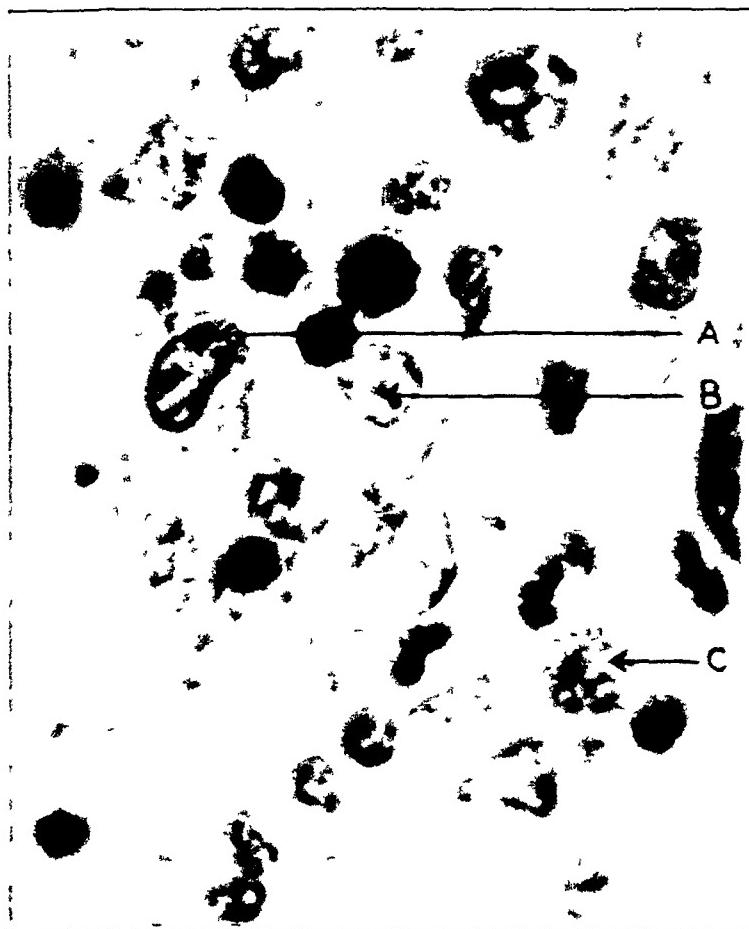


Fig. 4.—A typical area showing the character and distribution of the leukemic cells in the interacinar connective tissue in the pancreas. Cells *a* and *c* are large eosinophilic myelocytes. Cell *b* is an immature lymphocyte. Stem cells are also present in this general area but their characteristics are not brought out by photomicrograph. Dividing cells with mitotic figures and degenerating cells with pyknotic nuclei can be seen.

leukemic cells of the same type as those found in the blood smears and interfollicular tissue.

In general myeloid cells and lymphocytes were diffusely arranged and mixed together in the interacinar connective tissue (Fig. 4).

Spleen.—Here as in the lymph node sections through different parts appeared somewhat different and two typical ones will be described.

1 The first typical section was one showing a general increase in the lymphoid tissue with a scarcity of pulp or interfollicular tissue. No definite follicles were seen but rather was there a large overgrowth of the lymphoid tissue, with large diffuse areas of lymphocytes which in a normal spleen would be follicles. These areas had arms, or branches extending out into the pulp connecting with arms of other similar areas forming a kind of a network. The diffuse lymphatic follicular

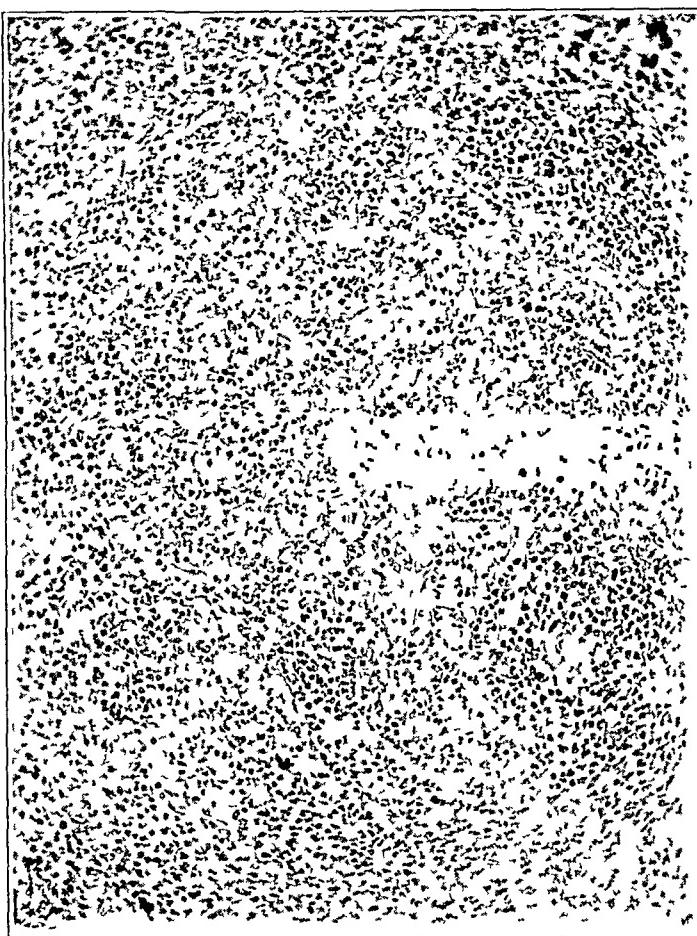


Fig 5.—A low power view of a typical area in the spleen, showing the general distribution of the cells. Note the absence of definite follicles and the general increase in the lymphoid cells. In the lower right hand corner can be seen a blood vessel with a condensation of lymphocytes about it.

tissue was in much larger amount than the pulp and the total amount of lymphatic tissue was greater than found in a normal spleen. In some areas, the line of demarcation between the pulp and these diffuse lymphocytic areas was more marked and easily definable. There were several hemorrhagic areas of various sizes, some being quite large. There were several areas of accumulation of lymphocytic cells along the course of the blood vessels, and when seen in cross-sections they appeared as fol-

icles, but on studying them more closely, it was easily seen that they were not typical. The predominating cell here, as elsewhere, was the medium size lymphocyte although there were many small and large types also.

However, in the areas of concentration of lymphocytes, I found eosinophilic and neutrophilic myelocytes as well as adult eosinophils. They were mixed diffusely with the proliferating lymphocytes. Myelo-

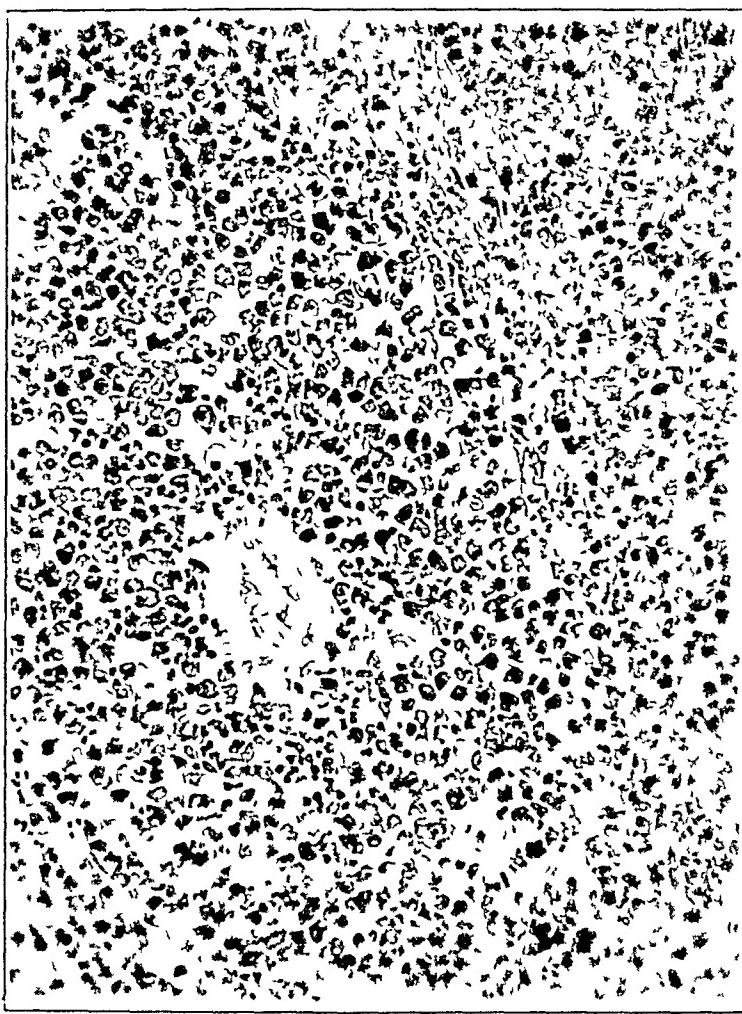


Fig 6.—Is a higher magnification of Figure 5. It is interesting to note that even in this area of condensation of lymphocytes, many myelocytes were found, although they cannot be distinguished at the magnification of this photomicrograph.

cytes were present, however, in larger numbers in the interfollicular tissue of pulp.

2 The other typical section was somewhat different. It showed an enormous amount of lymphoid tissue with very little pulp. Necrosis was more marked here. There were large hemorrhagic areas. Fibrosis was more extensive. Red blood cells were scattered diffusely throughout the lymphatic tissue. The predominating cell was the medium size

lymphocyte. Mitosis was occasionally seen. Some myelocytes and adult cells were seen but not so many as in the previous section. Some of these were also undergoing degeneration as indicated by their pyknotic nuclei.

In general, the lymphatic tissue predominated throughout the spleen although in some areas the pulp was much more in evidence than in others. There were several small areas seen where the pulp predominated. There was diffuse hypertrophy of lymphoid tissue throughout

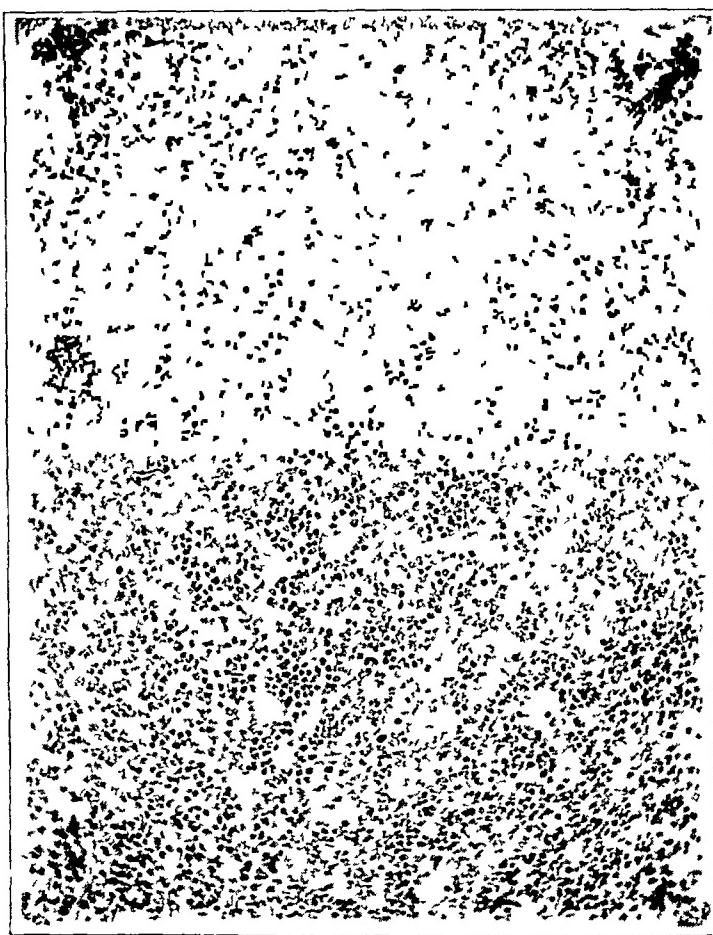


Fig. 7.—A low-power view of an area of the spleen where the pulp tissue slightly predominates, showing the diffuse distribution of the cells. Many myelocytes can be seen under high power oil immersion magnification but the medium-sized lymphocyte is the predominating cell. The border of a large hemorrhagic area in the upper portion of the field can be seen.

The malpighian bodies were apparently replaced by a concentration of lymphocytes along the course of the arteries. In cross-sections these appeared like malpighian bodies of the normal spleen, but they had no germinal center and were not so dense as normal follicles and contained relatively few small lymphocytes, most of them being medium, with a

few large ones. It was in these areas that the myelocytes were seen as well as in the pulp or interlobular tissue. On the whole, there was a total increase in the lymphatic tissue over that of the normal spleen. Myeloid metaplasia was present in these areas of 'lymphocytic concentration' but was much more extensive in the pulp. Lymphatic hyperplasia predominated (Figs. 5, 6 and 7).



Fig. 8.—A low-power view of the liver showing the interlobular leukemic cell infiltration and atrophy of some of the liver cells.

Liver.—The interlobular spaces were filled with leukemic cells and the latter filled many of the adjacent sinusoids. Otherwise, the sinusoids were free from cells. These masses of cells were composed mainly of lymphocytes in various stages of development. Some of them showed mitotic figures. Only an occasional myelocyte was found mixed in with the lymphocytes. Most of the lymphocytes were of medium size with relatively few large and small types. Degenerating forms with dense

pyknotic nuclei were seen. Mitosis was common. Necrosis of some of the cells was also found in areas but not to the extent found in other organs. Again we found cells here that had large nuclei with very little chromatin, a thin nuclear membrane and a few nucleoli. They had only a narrow rim of cytoplasm and were almost identical with the so-called "stem" cell as seen in the tissue (described before and found in other organs). Various stages of developing lymphocytes were found here. A few nucleated reds were seen with many adult red blood cells. No definite areas of hemorrhage were seen, however.

In general, there were extensive areas of leukemic infiltration limited to the interlobular spaces and a few adjacent sinusoids. The interlobular spaces were increased in size, which increase was probably due to pressure from the masses of leukemic cells. In some places the leukemic cells almost surrounded the lobules of the liver, making them very prominent. There was no local development of the cells in the sinusoids and they were not enlarged. There was no definite follicular arrangement of the leukemic cells (Fig. 8).

No sections of bone marrow were obtainable.

Blood Smears.—There were only two smears available to me for examination. One was taken on September 24, at which time the leukocyte count was 97,000. The other smear was taken on September 26, four days before death, which occurred on September 30. The leukocyte count was not taken at the time the last smear was made. It is interesting to note that the differential counts on the two occasions were quite different, the first one showing a predominance of the myeloid elements while the second one showed a relative increase in the young lymphocytes. I will first describe the more important cells seen before giving the differential counts of the different cells.

Blood Smear, Sept. 24, 1921.—On looking over this smear I was immediately impressed by the predominance of a cell which I wish to describe in detail. The size varied from that of a small lymphocyte to that of an ordinary large mononuclear cell. The nucleus was large and spherical and practically filled the cell leaving only a narrow ring of deep bluish cytoplasm, the latter occasionally containing vacuoles. Twenty per cent of these cells showed a peculiar type of azure granulation described by Pappenheim¹⁰ (Fig. 9 e).

The nucleus as described filled most of the cell, but the striking feature was the diffuse distribution of the chromatin. It was in the

10 Pappenheim, Atlas Die Zellen der leukamischen Myelose, Jena, Gustav Fischer, 1914. 1 "Stem" cells Plate XIV, Figs 1 and 27. 2 Myeloid azure granulation Plate XVIII, Figs 1 and 5. 3 Leukoblasts Plate XIV, Column B. 4 Promyelocytes Plate XIV, Column C, Rows a and b. 5 Micromyeloblasts (of Pappenheim) Plate XVI, Figs 12 and 13. 6 Myelocytes Plate XIV, Figs 11, 24, 48 and 73.

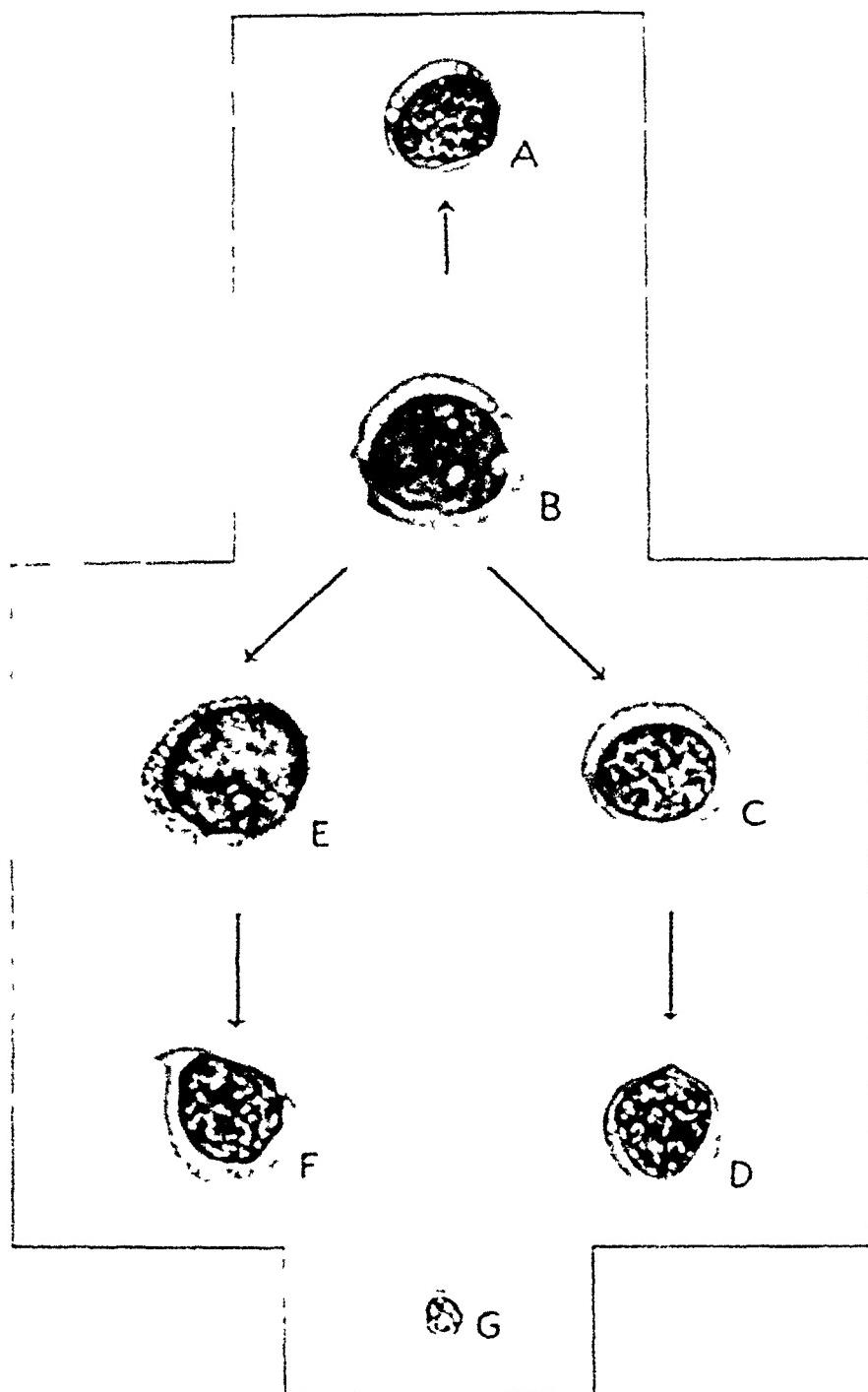


Fig. 9.—Drawing of cells from the blood smears. (a) Immature lymphocyte smaller type probably developing from a micromyeloblast (a cell similar to the one it only smaller). (b) Lymphoidocyte or "stem" cell. (c) Immature lymphocyte representing an early stage of development from type of cell as shown in (b). (d) Immature lymphocyte representing a later stage of development than (c). (e) Leukoblast showing azuro granulation. It represents the first stage in the development of myeloid cells from the stem cell. (f) Promyelocyte a cell representing the second or later, stage in the development of myeloid cells. (g) A Sm II eosinophilic myelocyte seen in the intra-retinal connective tissue of the macula. It is the same size as neighboring lymphocytes, with a nucleus identical in appearance with that found in these lymphocytes.

form of an extremely delicate network giving the nucleus the appearance of a fine mesh sieve. Many of the cells contained nucleoli, but not all, and when present they varied in number. Thirty-four per cent of the cells counted were of this type. This cell corresponded to the so-called lymphoidocyte of Pappenheim¹⁰ as shown in his atlas, and in Figure 9 *b* accompanying this paper.

The next most common cell (15 per cent) was one about the size of a small lymphocyte, having a very narrow ring of basophilic cytoplasm; in fact, in many instances the cytoplasm could not be seen at all, the nucleus apparently entirely filling the cell. The nucleus itself was rich in chromatin but the latter was evenly distributed throughout the nucleus with no areas of condensation. Occasionally a nucleolus was present. This cell corresponds in every detail with the micromyeloblast of Pappenheim¹⁰.

There were a number of cells which greatly resembled the previously described, so-called "stem" cell, but the chromatin was not so finely distributed and showed a tendency to form in strands. There was also a greater proportion of cytoplasm in the cell, the latter not containing, as a rule, so many of the coarse, azure granules. Nucleoli were seen but they were not so many or so distinct as in the stem cells. This type of cell I interpret as a leukoblast. Five per cent of the cells present were of this type¹⁰ (Fig 9 *e*).

Other somewhat similar cells with more abundant, but not so basophilic cytoplasm showed beginning acidophilia in some places. The nucleus was not so large in proportion to the amount of cytoplasm and was usually not spherical. The characteristic feature of this cell was also the "network" distribution of the chromatin in the nucleus. It was also formed in strands, but these were much coarser than in the case of the leukoblasts. The network might be compared to a very coarse, heavy mesh sieve. Nucleoli were rare, although occasionally seen, as was the case with the coarse, azure granules. The distinctive point of difference between this cell and the leukoblasts was the more marked coarseness of the strands of chromatin and the beginning acidophilic staining of the cytoplasm. This cell corresponded to the promyelocyte and was present in the same percentage as the leukoblasts¹⁰ (5 per cent) (Fig 9 *f*).

Myelocytes of all types, neutrophilic, eosinophilic and basophilic were present. Some cells, however, showed an apparent unequal maturing of the cytoplasm and nucleus, for example, the nucleus would be in the promyelocyte stage and the cytoplasm contain typical myelocytic granules, and vice versa. Fully differentiated typical neutrophils, eosinophils and basophils were also present. Some of the neutrophils were apparently degenerated as indicated by pyknotic nuclei. The adult cells

were of varying sizes. It was very easy to pick out a series of myeloid cells in all stages of differentiation from the stem cell to the full-grown adult neutrophil or eosinophil.

The lymphocytic series was also well represented in this smear with examples of the various stages of development. The earliest type found was one which resembled a stem cell only the cytoplasm was larger in amount and of a lighter blue color, and the azure granules were not so abundant and were finer, non-tangulai and of a pinkish-red rather than the deep purple of the stem cell. The distribution of the chromatin was the most characteristic point of distinction. Here the chromatin was more abundant, took a deeper stain and was spread over the nucleus in a manner which one might describe as blotchy, there being areas of condensation of chromatin. As a whole the distribution of the chromatin in the nucleus had a spotted appearance in counter distinction to the fine network in the stem cell or the coarser sieve-like appearance in the leukoblasts (Fig. 9-c).

From this early type could be traced a series of developing lymphocytes to the mature form as seen in normal blood but the various stages could not be so easily distinguished or defined as in the myeloid series. Progressive differentiation was characterized by an increase in the amount of chromatin, in its blotchy distribution and by an increase in the relative amount of cytoplasm which took a lighter bluish stain. There were many examples of the large typical adult lymphocyte which needs no description (Figs. 9-e, c and d).

In addition to the foregoing described types of cells there were some which could not be classified definitely because of their atypical appearance and so were not included in my differential count. If they had been I would have put them in an indeterminate group. The main difficulty in classifying them was owing to the fact that they had some characteristics of the myeloid type of cells as well as of the lymphocytes. For example, the cell would have a lobulated nucleus like that of a late myelocyte or early adult neutrophil but the cytoplasm of a lymphocyte and vice versa. There were some cells seen which had the characteristics of a myelocyte but the granulation was atypical. Of course, there were degenerating cells of all types especially the neutrophils, which showed very pyknotic nuclei.

The red cell series was like that in any typical case of acute leukemia with nucleated cells in various stages of development and many non-nucleated cells showing marked polychromatophilia, anisocytosis and poikilocytosis. Most of the cells showed pale centers and were poor in hemoglobin. Mitosis was occasionally seen in the blood.

The later blood smear which was at my disposal for examination showed the same types of cells as before described, only in different proportions. Here it is interesting to note that there was a relative

decrease in the myeloid elements of the blood with an increase in the immature lymphocytes. In this blood smear the series of developing lymphocytes could be more easily made out than in the previous one, beginning with the stem cell and ending with the adult lymphocyte. The differential counts of the two blood smears are given below.

TABLE 1—*First Smear, Taken Sept 24, 1921 Differential Count (300 Cells)*

	Per Cent
Large lymphocytes	2.00
Small lymphocytes	13.3
Large mononuclears	None
Transitional	1.00
Neutrophils	3.7
Neutrophilic myelocytes	10.00
Eosinophils	1.3
Eosinophilic myelocytes	1.7
Basophils	0.7
Basophilic myelocytes	0.3
Micromyeloblasts	15.00
So-called "stem cells"	34.00
Promyelocytes	5.00
Leukoblasts	5.00
Immature lymphocytes	7.00

TABLE 2—*Second Smear, Taken Sept 26, 1921, Differential Count (300 cells)*

	Per Cent
Large lymphocytes	2.5
Small lymphocytes	22.00
Large mononuclears	0.5
Transitional	0.5
Neutrophils	2.5
Neutrophilic myelocytes	3.00
Micromyeloblasts	17.00
So-called "stem cells"	7.5
Promyelocytes	7.5
Leukoblasts	2.00
Immature lymphocytes	35.00
No eosinophils or basophils or their myelocytes	

Before reviewing the previously reported cases of so-called mixed leukemia, I will review briefly the important points in my own case which have led me to believe that I am dealing with a case of true mixed leukemia.

First, let me condense the important findings in the blood smears. These are not only interesting but very striking. Their importance cannot be exaggerated, as it was by means of examination of the blood smears that the true condition was first appreciated. On the first examination of the blood smears by Dr Gardner, the condition appeared to be one of acute myeloid leukemia, but even he noted that the lymphocytes were very hard to differentiate from cells in the myeloblast stage.

Without careful study and working out a typical series, beginning with the stem cell and ending with either the adult lymphocyte or granular leukocyte, it would be difficult to determine the true condition present. The most important discovery in the examination of the smear was the presence of both types of immature cells, that is, the lymphoid and myeloid forms. It was this feature that attracted the attention of Dr. Downey when he examined the smear, and he was the first one to appreciate and interpret their importance and to realize that here was a probable case of true mixed leukemia. More careful study of the blood smears only emphasized the facts already stated—that on the one hand there was a complete series of cells representing the various stages of myeloid development from the original stem cell to the full-grown granular leukocyte, and on the other hand just as definite a series could be found showing developing lymphocytes beginning with the same stem cell and ending with the typical completely differentiated lymphocyte. A few atypical cells were present, but their importance will be discussed a little later on.

The other important point to note about the blood was that in the earliest smear the myeloid element of the blood predominated while later on as death approached, the lymphoid and myeloid elements played a more equal part with the former slightly predominating.

The more important gross pathologic findings were a greatly enlarged spleen, petechial hemorrhages scattered throughout the body, marked enlargement of many of the mesenteric and pre-aortic lymph nodes, a leukemic polypoid mass in the cecum, and kidneys showing evidence of leukemic infiltration. From the gross findings, one might easily consider the case as that of a simple acute myeloid leukemia.

SUMMARY OF MICROSCOPIC FINDINGS

The most important feature of the involved lymph nodes was a disappearance of the typical follicle, probably due to a general increase in the lymphatic tissue which was spread out over the entire section. Lymphoid hyperplasia was the predominating feature, but myelocytes were found in the interfollicular tissue, in rather large numbers in some areas.

The reticular tissue of the alveolar walls in the lungs showed typical myelocytes and immature lymphocytes mixed together in the various stages of development. This local development of myelocytes and lymphocytes in the same areas almost side by side strongly points to a condition of mixed leukemia.

The same condition was found in the kidneys in the areas of leukemic cell infiltration, but was even more marked here than was the case in the lung tissue.

The findings in the pancreas emphasize the same thing, and here again we found myelocytes and immature lymphocytes side by side in the interacinar connective tissue, and in addition, cells of the myeloblastic type. The similarity in the nucleus of some of the eosinophilic myelocytes with those of the adjacent lymphocytes suggests that they may originate from the latter.

Again in the spleen we found evidence of myeloid and lymphoid metaplasia going on not only side by side but actually mixed together. There was an increase in the lymphatic tissue in general, with a replacement of the normal follicles by huge masses of lymphoid tissue. Concentration of lymphoid tissue about some of the large blood vessels suggested follicles when seen in cross section. The pulp tissue predominated in certain areas and here the myeloid metaplasia was more in evidence, but myelocytes were also frequently found mixed in with the masses of lymphoid cells. Nowhere was there a distinct line of demarcation between the lymphoid and myeloid activity.

The findings in the liver resembled very closely those of ordinary acute lymphatic leukemia, with the interlobular spaces filled with leukemic cells and the sinusoids free in general, with only a few myelocytes.

The lymphoid picture predominated in the leukemic infiltration in the polypoid mass found in the intestines. Evidence of degeneration found in the various organs was no different than that met with in ordinary cases of acute myeloid or lymphatic leukemia.

Viewing the situation as a whole we found some of these organs showing a predominance of myeloid activity, while the lymphoid elements were more in evidence in others, but both were definitely present in all with the possible exception of the liver and the polypoid mass in the intestines. There was evidence of irritation of both systems in all the organs examined. (It is regretted that the bone marrow was not obtainable for study in this case.) But most important to note was the mixing together or diffusion of the immature cells of both systems, with no definite line of demarcation between the two. It was because of this persistent striking feature that I feel justified in calling this case one of true mixed cell leukemia.

LITERATURE

Before going into detail in the discussion of the evidence present in this case in favor of a true mixed cell leukemia, I should like to review briefly previously reported cases bearing this name. Although there were several cases of atypical or mixed cell leukemia recorded in the literature before Turk¹ reported his case in 1906, he was the first to publish what he believed to be a case of true mixed leukemia. This case began with a typical picture of a myeloid leukemia both from a clinical standpoint and a microscopic study of the blood. The spleen was

greatly enlarged, the lymph glands normal in size. The leukocyte count went up as high as 373,000 with 90 per cent myelocytes. Under intense arsenic therapy the leukocyte count dropped until it reached a stage of almost a leucopenia. At one time there were only 3,500 cells counted. About eight months after the disease started the picture began to change. Clinically, the lymph glands began to enlarge and the blood picture showed an increasing number of large atypical nongranular cells, with a single nucleus which often showed pale nucleoli (immature lymphocytes). The percentage of myelocytes in the blood decreased. Turk speaks of these cells as being of the character of lymphoid cells found in acute lymphomatosis. Shortly before death, these cells formed 20 per cent of those present while there were only 3 per cent myelocytes. He believes that the lymph glands were in a stage of at least temporary acute leukemia. He closes his report by saying that here he has a case of chronic myeloid leukemia where eventually an acute lymphoid leukemia entered. He suggests a possible cause for the entrance of the lymphoid leukemic process, saying that it may be due to an exhaustion of the myeloid elements.

Although it appears that Turk had a mixed form of leukemia, he did not have histologic studies of the organs to verify it. This is the main argument of Naegeli, Pappenheim,¹¹ Meyer, Heineke, von Domarus and others who disagree with him. Naegeli¹² states that histologic studies of such a case might show the apparent lymphoid tissue to be myeloid tissue. Fleischman¹³ believes his case was myeloid leukemia with an increase in proportion of lymphocytes in the blood because of a deficiency in the bone marrow. Herz³ believes that the existing stimulation producing activity of one type of tissue could cause an activity of the other type as well. Turk reported several other cases similar to the one described above.

Hirschfeld² was the only one who thought that Turk had a case of the true mixed form of leukemia, and gave for further proof of the existence of this type a report of a case seen in 1909. The leukocyte count was 34,000 with the percentage of lymphocytes varying from 55 to 89 per cent. He found lymphadenoid metaplasia of the bone marrow along with myeloid metaplasia of the lymph glands and spleen pulp with a blood picture of lymphocytic leukemia. Many nucleated reds were found in the lymph glands. He felt that the lymphatic leukemia in this case was primary and probably the source of the myelogenous activity.

11 Pappenheim, A. Bemerkungen zur Frage der akuten Myeloblastenleukämie und Leukosarcoma, Wien klin Wechschr **25** 163, 1912.

12 Naegeli, O. Blutkrankheiten und Blutdiagnostik, Ed 2, Leipzig, Veit and Company, 1912.

13 Fleischman, P. Der zweite Fall von Monocyten Leukämie, Folia Haematol **20** 17, 1915.

The bone marrow changes probably occurred first, as shown by the early marked anemia, then, changes occurred in the spleen and liver, and last in the lymph glands. He believes his case to be an example of a true form of mixed myelogenous and lymphatic leukemia. His findings of myeloid metaplasia in the splenic pulp and lymph glands was similar to what I found in my own case. In conjunction with the lymphadenoid metaplasia, which he found in the bone marrow, and the blood picture, I believe that he is justified in calling his case one of true mixed leukemia. Hirschfeld also showed that there was a continuous series of transitional forms leading from the typical acute lymphocytic leukemia to the acute mixed cell type of leukemia. (He modified this observation later.) Meyer, Heineke, Fabian, Naegeli, Schatloff and Pappenheim disagree with Hirschfeld and claim that the myeloid tissue in his case was squeezed out of the bone marrow through hyperlymphadenoid activity, and was thus transplanted into other places where it proliferated viciously in the extramedullary organs.

In 1909, Herz³ reported a case. The clinical symptoms were those of acute leukemia with enlargement of the lymph glands on the right side of the neck and no enlargement of the spleen. There were 51,000 leukocytes and 45 per cent nongranular cells with large single nuclei. In later counts the neutrophilic myelocytes increased from 5 to 16 per cent and the large nongranular cells increased to 54 per cent. The histologic findings were as follows: the bone marrow showed an activity of the myeloid tissues with neutrophilic granular myelocytes and non-granular myeloblasts. In the middle of the myeloid tissue he found groups of cells that had all the characteristics of the small lymphocyte. They were the same type of lymphocyte as found in the follicles of the spleen. However, the border line between these "herds" or groups of lymphocytic cells and the myelocytes was rather sharp. The spleen showed typical myeloid changes in the pulp with suppression of the follicles, but the latter could still be seen although they were small. The lymph glands showed a picture often seen in chronic lymphatic leukemia with the structure gone, follicles and interfollicular tissue indistinguishable. Most of the cells were proliferating lymphocytes. No germ center cells were seen. In the center of these condensations of lymphocytes, he found large cells with a single nucleus which he interpreted as neutrophilic myelocytes. In one pulmonary lymph gland he found a marked activity of the lymphoid tissue with a moderate activity of the myeloid element. The liver in this case showed small groups of so-called myeloblasts in the interlobular tissue. Herz calls his case one of mixed leukemia because of the simultaneous appearance of both types of tissues in the bone marrow, with a definite diffuse myeloid hyperplasia and lymphatic activity, and further because of the myeloid metaplasia in the

spleen and lymphoid metaplasia in the lymph glands, the latter also showing myeloid metaplasia.

Von Domarus⁸ agrees with Heiz in his diagnosis, but Naegeli⁷ again disagrees, saying that the appearance of the myeloid cells was agonal or a dispersion of marrow cells due to sepsis, as an endocarditis was found at necropsy. Heiz admits that sepsis can explain the acute lymphatic leukemia followed by a myeloid leukemia but he does not believe it can explain a myeloid metaplasia in the bone marrow, spleen and lymph glands as was found in his case. Heiz concludes by stating the fact that, along with many lymphocytes an important number of the elements of myeloid tissue was present in the blood, and in addition, activity of both types present in the hematopoietic organs proves that there must be a disease of both types of tissue that is, a mixed leukemia. It was these facts that made Heiz call his case mixed leukemia.

The next case of mixed leukemia was that reported by Herxheimer.⁴ The white count was 72,000. The differential showed most of the cells to be small lymphocytes but with 25 per cent myeloblasts. He also found many small cells with a single nucleus which stained very dark and had little, if any, structure. They had a very narrow cytoplasm. He interpreted these as being nucleomeloblasts or very young, small lymphocytes. He interpreted the large cells, with a single nucleus having a distinct clear fine structure and many nucleoli, as being myeloblasts. Most of the cells in the bone marrow were lymphocytes but there were some myelocytes and developing red blood cells. The extra-medullary organs showed evidence of myeloid and lymphatic activity. Necropsy showed no evidence of sepsis, but a large leukemic mass in the mediastinum in which the thymus was obliterated. He concludes that his case could be interpreted as one of the small cell leukemias if it were not for the presence of myelocytes in the various organs, even including the mediastinal tumor. He believes that first there was a lymphatic leukemia and later the entrance of a myeloblastic leukemia with a tendency toward tumor-like activity, especially in the mediastinum, and that his case, like those of Hirschfeld and Heiz, is an example of true lymphatic and myeloid leukemia.

Naegeli⁷ and his followers, not believing it is possible to have a mixed leukemia, explain Herxheimer's case on the basis of a compensatory activity of the "stem" cells, or immature leukocytes following their expulsion from the bone marrow, as is observed in lymphatic leukemia and toxic anemia. They again offer the explanation that the myeloid cells are the result of a vicarious activity of displaced bone marrow myeloid tissue in the extra-medullary organs. Herxheimer does not believe that his case can be explained by a simple passing out of cells into the blood, as was spoken of in Heiz's case, as there was no septic cause for this in his case. He does not see where the proof has been

given for Naegeli's idea of the vicarious activity of displaced bone marrow myeloid tissue, and that this idea is no better than his own, namely, that this case is one of a true mixed leukemia. He does not believe that we can definitely say whether it is a vicarious activity or not until we know the cause and origin of leukemia. Because of the distinct separation of the local development of the lymphocytes and granular leukocytes, even though they are side by side, the farthest he wants to go is to call his case one of combined leukemia, and he leaves the question open as to the cause of the appearance of the latter form of leukemia, in his case the myeloblastic leukemia, that is, whether it is a compensatory entrance or not.

De Castello¹⁴ reports a case of mixed leukemia, where a leukopenia developed under the use of roentgen ray and lymphocytes entered. Naegeli and Pappenheim¹⁵ explain this by assuming that there was a de-differentiation of the myeloid cells.

In 1905, Browning¹⁶ reported a case which he called mixed cell leukemia. The leukocyte count a few weeks before death was 98,300, with a differential count of 12.8 per cent neutrophilic myelocytes and transitionals, 38 per cent neutrophilic polymorphonuclear leukocytes, 4.5 eosinophilic myelocytes, basophilic cells 2 per cent, large nongranular, 40.7 per cent, small nongranular 4 per cent. Seventeen normoblasts were seen while counting 1,450 leukocytes.

He described a typical eosinophil with peculiar fine, pink granules that are very scanty, also cells in every way like the large nongranular elements except that they contained coarse, spherical, basophil granules which were numerous. The author concludes from his observations on the origin of granular leukocytes in the human fetus, previously referred to¹⁶ that such appearances indicate a reversion to fetal conditions, the large nongranular basophil cells being due to reversion of the granular myelocytes to undifferentiated leukoblasts, or to hyperplasia of the few such cells normally present in the adult marrow, with the resumption of the embryonic capacity for secreting granules.

In addition to the previously described cases of mixed leukemia, there are many cases of atypical leukemia recorded in the literature. I have picked out a few of them which may have some of the features of mixed leukemia, and may possibly fall into this classification.

In 1915, Krjukow¹⁷ reported a case of acute microlymphoidocytic leukemia, in which there was hyperplasia of the follicles of the spleen.

14 De Castello Quoted by Herxheimer, Footnote 4

15 Naegeli, O., and Pappenheim, A. Quoted by Herxheimer, Footnote 4

16 Browning, C. A Case of Mixed-Cell Leukemia with a Short Account of Recent Views on Atypical Leukemias, *Lancet* 1: 507 (Jan.) 1905

17 Krjukow, A. Ueber einen Fall von akuter Microlymphoidozyten-Leukämie, *Folia Haematol* 15: 328, 1915

and lymph glands and a distinct development of myeloid tissue in the spleen. The patient improved so far as the leukemia was concerned but died of an intercurrent pneumonia.

Michaelis¹⁸ found evidence of the differentiation from nongranular cells (probably immature lymphocytes) to fine granular types in the blood of a patient. The spleen showed large nongranular mononuclear and giant cells with similar types found in the bone marrow, liver and lymph glands.

Simon¹⁹ reported a case with myeloid elements predominating in the blood at the onset, with decrease in the myeloid elements as death approached and a relative corresponding increase in lymphocytes.

A differential count on two of Wolff's²⁰ cases showed 78 per cent nongranular cells, probably immature lymphocytes, with 17 per cent myelocytes.

Klein and Steinhaus²¹ report a count of 41,000 leukocytes, 66 per cent of which were lymphocytes and 17 per cent myelocytes. The myelocytes formed a greater part of various tumor masses throughout the body, but were not present in the spleen or the lymph glands.

In a case of Fowler's,²² 50 per cent of the cells were large non-granular types undoubtedly immature lymphocytes, with 12 per cent myelocytes.

Wilkinson²³ reports a case which began as a typical myeloid leukemia, but later immature lymphocytes appeared in the blood. These increased in number as the disease continued and were quite numerous shortly before death. It is important to note that in this case "the peculiar feature of the blood was that lymphocytes were quite as numerous as myelocytes and there was every gradation between the two. All types of nucleated red cells were present." The last blood smear taken showed an amazing typical lymphocytosis though myelocytes were present.

Thus at first, there was a myelocytosis with lymphocytes in moderate proportion, while later a lymphocytosis with numerous myelocytes.

18 Michaelis, L. Ueber einen der Gruppe der Leukämie-artigen Erkrankungen zugehörigen Fall, *Ztschr f klin Med* **45** 87, 1902.

19 Simon, C E. A Case of Myelogenous Leukemia with Severe Unusual Features (Absence of Eosinophilic Leukocytes), *Am J M Sc* **125** 984, 1913.

20 Wolff, A. Ueber der Bedeutung der lymphoid Zelle bei der normalen Blutbildung und bei der Leukämie, *Ztschr f klin Med* **45** 385, 1902.

21 Klein and Steinhaus. Ueber das Chlorom, *Centralbl f allg Path u path Anat* **15** 49, 1904.

22 Fowler, J S. On the Occurrence of a Form of Leukemia Intermediate in Type Between the Lymphatic and the Splenomedullary Forms, with Notes of a Case in a Child Five Years Old, *Internat Clin* **3** 217, 1903.

23 Wilkinson, R. A Case of Leukemia with Change of Type in the Appearances of the Blood, *Lancet* **1** 1739 (Jan.) 1903.

present It is apparent that the abnormal leukocytes present had undergone a complete change This case resembles mine in that the myeloid leukemia predominated early while lymphocytic activity increased later From the foregoing description, I believe Wilkinson's case became eventually one of true mixed leukemia

DIFFERENTIAL DIAGNOSIS

Fabian, Naegeli and Schatloff⁶ define the acute lymphatic and myeloid types in their paper on leukemia They also emphasize the point that in the beginning of acute lymphatic leukemia there is a certain small percentage of myelocytes in the blood which are crowded out of the bone marrow, due to the abnormal lymphatic proliferation there The authors say these diminish rapidly as the disease progresses

It is important to note in this regard that, although myelocytes may be found in the blood when any great demand is put on the bone marrow, promyelocytes and leukoblasts never appear unless there is a definite specific stimulation of the bone marrow, or extramedullary organs such as is found in myeloid leukemia

The same can be said in reference to the lymphocytes in myelogenous leukemia, for here, although lymphocytes are found in the blood, the immature forms described by Naegeli are not found in the blood unless there is stimulation of the lymphatic tissue similar to that producing the activity of the myeloid tissue

It is important that the diagnosis of leukemia should not depend on the blood findings alone The case should be considered as a whole including the clinical picture as well as the histologic study of the various organs involved This point was clearly shown in Pappenheim's case of myelogenous leukemia where the only changes present were in the bone marrow Meyer, Heineke and Butterfield²⁴ reported a case of myelogenous leukemia with no changes in the bone marrow (both cases were referred to by Werzberg²⁵)

Pappenheim,²⁶ Walz²⁷ and Dennig²⁸ have reported cases which hematologically were lymphatic leukemia, yet in these cases the spleen and lymph nodes were not involved, but the bone marrow showed some lymphocytes

24 Butterfield, E., Heineke, A., and Meyer, E. Ueber das Vorkommen der Altmannschen Granulationen in den weissen Blutzellen, *Folia Haematol.* 8:337, 1909

25 Werzberg, A. Neue experimentelle Beitrage zur Frage der myeloiden Metaplasie, *Virchow's Arch f path Anat.* 204:272, 1911

26 Pappenheim, A. Zwei Fälle akuter grosszelliger Leukämie, *Folia Haematol.* 4:301, 1907

27 Walz Quoted by von Domarus, Footnote 8

28 Dennig, A. Ueber akute Leukämie, *Munchen med Wchrsschr.* 47:1297, 1900

So the importance of a complete study of a case is evident. It was because Turk did not have any histologic studies to accompany his case of so-called mixed leukemia that he was criticized in making his diagnosis.

The importance of nucleoli as the distinguishing factor between the early types of lymphatic and myeloid cells has been greatly studied and discussed, but the present day viewpoint accepted by most hematologists is that they are worthless as a means of differentiation. Buttefield and Pappenheim²⁹ found that the number present varied so greatly that it was of no significance. Naegeli,¹² however, believes that myeloblasts can be differentiated from lymphoblasts by the number of nucleoli, there being more in the case of the myeloblasts.

With regard to the oxydase reaction, Pappenheim and Dohre⁹ conclude regarding it that "it does not indicate an absolutely unfailing histogenetic difference between two heterogeneous cell races."

We cannot depend on the presence and character of azure granules in the cells as a sure means of differential diagnosis between myeloid and lymphoid cells. Hyneke³⁰ gives a comprehensive review of the literature up to 1912. Lippman, in an unpublished paper, reviews the literature up to 1922 and his conclusions are that, taken as a whole, azure granules are of no value in distinguishing between myeloid and lymphoid cells. However, he admits that the coarse, angular, purple granules described by Pappenheim as characteristic of the myeloid stem cell are only rarely found in lymphocytes and are numerically much less in the latter. The azure granules of lymphocytes are much finer and more reddish in color.

Hyneke, in his discussion of granules, states that he has found cells with both neutrophil and azurophil granules in an acidophilic cytoplasm. He disagrees with Gravitz and Pappenheim, whom he quotes, as saying that azure granules never occur except in a basic cytoplasm.

With the foregoing discussed points in mind, let us determine the classification of my case. The smear showed, as noted before, all stages of developing myeloid cells from the original stem cell of Pappenheim to the fully differentiated granular leukocyte. For this reason the case could not be classified under the heading of simple lymphatic leukemia. Naegeli might explain the presence of myelocytes through forcing out of bone marrow tissue into the blood, but I am sure that he would not feel that this argument would hold true where promyelocytes and leukoblasts were present, as well as stem cells with the typical myeloid type of granulation of Pappenheim.

²⁹ Pappenheim, A. Bemerkungen über aetiologische Unterschiede, usw., der lymphoiden Zellformen des Blutes, *Folia Haematol* **9** 321, 1909.

³⁰ Hyneke, K. Fur Monozytenfrage, *Folia Haematol* **13** 345, 1912.

For practically the same reason the case could not be classified from the blood findings as simple myelogenous leukemia, for, as noted before, immature lymphocytes in various stages of development were present in all smears, even predominating in the later one. The blood picture in my case resembled very much that found by Turk in his first case. From the findings I cannot classify it as simple lymphatic or simple myelogenous leukemia, for there is a mixture of both types present, the latter predominating first and the former predominating later. So the blood findings indicate to me that my case is one of true mixed leukemia.

Histologic examination of the tissues does not allow me again to consider the case as a simple one of either type, but as a mixture of both, except in the case of the liver and the intestinal polypoid mass. The latter two, if considered alone, favor lymphatic leukemia, as the findings here are quite typical of this condition. This point, however, considered along with definite evidence of myeloid metaplasia in all the other organs examined, only emphasizes the fact that here we are dealing with a mixture of the two types.

Sections of all the other organs studied showed evidence of activity of both systems. Lymphoid metaplasia predominated in the spleen, yet there were areas where the myeloid activity was more in evidence. In these areas, the pulp also predominated. Myelocytes were even found in the areas of condensation of lymphocytes about some of the blood vessels, as described before. Some of these myelocytes had a small, dark-staining nucleus positively indistinguishable from the nuclei of some of the surrounding lymphocytes. The fact that the follicles had disappeared, and in some cases showed evidence of atrophy, as well as the fact that myeloid metaplasia was so much in evidence, make it impossible to classify this case as a pure lymphatic leukemia. Also the fact that there was a total increase in lymphatic tissue over that of a normal spleen, and the presence of large areas of concentration of lymphocytes, probably replacing the malpighian bodies, forbids placing it in the category of simple myelogenous leukemia.

The above statements hold true for the lymph glands as well as the spleen. Again, many of the myelocytes found in the lymph nodes had small dark nuclei, rich in chromatin, which were identical with those of adjacent lymphocytes. It would appear that they have a common origin, or better, that the myelocytes develop from the lymphocytes.

In reviewing the lung, kidney and pancreas findings the important fact to note is that both myeloid and lymphoid metaplasia was much in evidence in these organs. The local development of myelocytes and immature lymphocytes was common. The developing cells of both systems were mixed diffusely together with no definite arrangement and no evidence of separation of the two systems.

Because of this diffuse mixing together of lymphoid and myeloid elements in the various extramedullary organs, I have another strong reason for classifying my case as one of true mixed leukemia.

Myelocytes have been found in lymphoid organs in other instances, aside from cases of myelogenous or mixed leukemia.

Citron³¹ and Fineman³² reported cases where they found myeloblasts coming right out of the follicles in the lymph nodes.

MacCallum³³ would say that these cells were transplanted from the bone marrow and grew in the extramedullary organs. Naegeli⁷ believed the same until recently, but now he admits that myeloid cells can develop from what he calls undifferentiated mesenchymal cells which occur about the blood vessels in extramedullary organs. However, he admits in his last textbook that these undifferentiated cells can develop into either lymphoid or myeloid types. He admits in this statement that there is a common mother cell of the two types under certain circumstances.

Meyer and Heineke⁵ state that myeloid tissue in lymphatic organs does not arise from the lymphocytes in the follicles, but from an undifferentiated element similar to the lymphoid cells of bone marrow.

Sternberg³⁴ claims that the follicles and pulp strands can be enlarged in myelogenous leukemia so that the border between the follicles and the pulp is wiped out or indistinct. He has found myelocytes in the follicles.

Fabian, Naegeli and Schatloft⁶ state that study of the intermediate forms between the earliest types of immature cells and the adult cell is necessary in order to classify the unique cells. For example, in the case of myeloid leukemia, intermediate forms between the myeloblasts and the myelocytes should be present in large numbers. They also mention the appearance of a large number of nucleated red blood cells in myeloid leukemia.

Using this as the criterion, it is evident that there was definite leukemic activity of both systems in my case.

The above citations, in correlation with the previously reviewed cases of mixed leukemia, in addition to my own case, are evidence enough, I believe, that myelocytes may develop along with lymphocytes in lymphoid organs, in spite of the fact that Naegeli and his followers insist that the two systems are entirely separate, and are never mixed or found together in the true sense of the word.

31 Citron, J. Ueber zwei bemerkenswerte Fälle von (akuter) Leukämie, *Folia Haematol* **20** 1, 1915.

32 Fineman, Solomon. A Study of Microlymphocytic Leukemia, *Arch Int Med* **29** 168 (Feb.) 1922.

33 MacCallum, W. G. *Text Book of Pathology*, Philadelphia, W. B. Saunders Company, 1917.

34 Sternberg, C. Leukosarkomatose und Myeloblastenleukämie, *Beitr z path Anat u z allg Path*, Jena **61** 75, 1915.

Let us now consider some of the objections to the diagnosis of mixed leukemia which have been made by various men

Naegeli,⁷ of course, as well as his followers, insists that it is impossible to have a condition of mixed leukemia. They believe that the two systems, lymphatic and myeloid, are separate and distinct with a separate stem cell for each type from which the adult cells develop. They believe it is impossible to have a mixed form. The question whether or not there is a separate mother cell of the two types or whether they may develop from a single common mother cell will be discussed a little later in the paper.

Several objections or questions have been raised regarding previously reported cases of mixed leukemia.

Naegeli objects to Herz's case, claiming that the appearance of the myeloid cells was caused by displacement of marrow cells, due to sepsis, as an endocarditis was found at necropsy. Herz's answer to this objection has already been given in the previous discussion of his case. In regard to my own case there was no evidence of sepsis either from the clinical history, physical examination or at necropsy. Even if there had been, I do not believe that sepsis can explain the appearance of either the lymphoid or the myeloid metaplasia which was so very definite and prevalent in the spleen, lymph nodes, lungs, kidneys and pancreas.

Turk,³⁵ in 1907, reported two cases of septic disease with lymphemic blood findings. The first case showed 90 per cent lymphocytes, and a diagnosis of lymphatic leukemia with secondary sepsis was made. Necropsy showed a septic endocarditis, and almost entire withering of the granulocytes in the bone marrow with replacement by lymphocytes. This was not considered a case of leukemia.

The second case showed leukocytosis with 62 per cent lymphocytes. A diagnosis of lymphatic leukemia with secondary sepsis was made.

Erb³⁶ reports a case of lymphatic leukemia in which a secondary septicemia later developed. There were 91 per cent lymphocytes and only 0.5 per cent myelocytes. Tissue sections showed a lymphatic metaplasia in all the blood forming organs.

Eppenstein³⁷ discussed the question of acute leukemia with "Streptokokkensepsis" and reports several cases. He believes that the sepsis was the secondary invader. He refers to cases by many other authors including Vogedes, Frankel, Jousset, Holst, Ziegler and Jochman who report cases similar to his, with a positive blood culture. The path of

35 Turk, W. Septische Erkrankungen bei Verkummerung des Granulozytensystems, Wien klin Wchnschr 20: 157, 1907.

36 Erb, W. Septische Erkrankungen und akute Leukämie, Deutsch med Wchnschr 33: 833, 1907.

37 Eppenstein, H. Akute Leukämie und Streptokokkensepsis, Deutsch med Wchnschr 33: 1984, 1907.

entrance of the streptococcus could not be found, however, in Eppenstein's case. Even the tonsils, which are usually swollen in leukemia, were unchanged. The blood count in his case showed 96 per cent lymphocytes. No myelocytes were found in the blood.

Naegeli as quoted by Eppenstein, reports a case of chronic lymphatic leukemia where streptococcal sepsis appeared shortly before death. Although myelocytes appeared in the blood, no younger cells than these were found and the myelocytes were present only in a very small percentage.

It is evident from the study of the preceding cases that sepsis alone will not produce a lymphatic metaplasia in the bone marrow, or myeloid metaplasia in the lymphoid organs where the opposite condition was primary and preexistent. In other words add sepsis to an existing acute lymphatic leukemia and myeloid metaplasia will not appear in the extramedullary organs. Sepsis may cause the appearance of myelocytes in the blood in a case of acute lymphatic leukemia, but it never has been shown to produce myeloid metaplasia in the extramedullary organs.

Von Domarus⁸ believes with Naegeli that one can get the same changes in a myeloid organ from sepsis as one can get in a myeloid leukemia, and quotes Meyer and Heineke as believing the same thing, and that it has been produced experimentally in animals. He refers here to the animal experiment of Rachzeh,³⁸ where lymphadenoid metaplasia of the bone marrow was observed. He also insists that the tissue reaction to bacterial toxins can be either myeloid or lymphatic in character.

However, the cases of sepsis and leukemia as reported in the literature which I have read do not coincide with these animal experiments. Blood and tissue changes somewhat leukemic in character produced in animals are very different from leukemia in human beings.

Another explanation which Naegeli gave for the appearance of the marrow cells in Herz's case was that it was agonal. I believe it is possible to have a few myelocytes thrown out into the blood, possibly as a compensatory effort on the part of the bone marrow, as death approaches, but the production of active metaplasia in the extramedullary organs is entirely unlikely.

Naegeli has also objected to the diagnosis of mixed leukemia, especially in the cases of Hirschfeld and Herxheimer, on the basis that the myeloid metaplasia, evidence of which was present in the blood smears and extramedullary organs, was due to displacement or transplantation of bone marrow tissue into the extramedullary organs, these myeloid cells having been forced out of the bone marrow because of the massive lymphatic infiltration with suppression of the myeloid activity there.

In speaking of Herxheimer's case, Sternbeig³⁴ suggests that there was a local diminished resistance in the mediastinal tumor, possibly due to focal changes, so that myeloid activity could enter and take hold.

So far as I could determine, no proof was given to substantiate either one of these ideas, while, on the other hand, definite instances of myeloid metaplasia had been found in the extramedullary organs as discussed before. Instances of this have also been found in conditions other than that of mixed leukemia.

Butterfield³⁹ found cases of masses of myeloid cells in the extra-medullary organs without hyperplasia of the bone marrow, and when he found myeloid tissue in the obliterated appendix and in granulation tissue, he had another good argument in favor of the local formation of myeloid cells, whether in the spleen, lymph glands or liver.

Werzberg²⁵ states that you may get myeloid metaplasia of the parts in cases of hyperplasia of lymph nodes. His assertion of the fact that lymph follicles are small and unseen and without germ centers in most cases of chronic myeloid leukemia does not indicate, however, that the lymphopoietic tissue was passive or was squeezed out or substituted by a myelopotent pulp tissue. But on the other hand, both pulp and follicles may react to the same poison by myeloid metaplasia or hyperplasia. It is evident that Naegeli's explanation need not always hold true.

Pappenheim⁹ claims that the myeloblasts present are the result of the differentiation of lymphocytes coming from lymphoid tissue. In the same way he explains the presence of the lymphocytes as the result of a backward differentiation of myelocytes to a primitive stem cell, and a forward differentiation into the various stages of developing lymphocytes to the mature adult cell. However, he can only offer this explanation by assuming a polyvalent stem cell which, of course, he does.

In my case de-differentiation of lymphocytes back to the stem cell and then to myelocytes, or vice versa, is possible, but it seems to me there is more evidence of a direct formation of myelocytes from lymphocytes as indicated by the great similarity between the nuclei of some of the myelocytes and lymphocytes. This was very noticeable in the spleen, kidneys, lungs, pancreas and lymph glands. In the interacinar connective tissue of the pancreas many very small eosinophilic myelocytes were noted, where not only the nuclei were identical with those of the small lymphocyte, but the actual size of both of the cells was the same, indicating that many of these small lymphocytes in the tissue differentiated directly into myelocytes and developed eosinophilic granules without any change in the size of the cell occurring (Fig. 9g).

39 Butterfield, E. Ueber die ungranulierten Vorstufen der Myelocyten und ihre Bildung in Milz, Leber und Lymphdrusen, Deutsch Arch f klin Med 92 336, 1907-1908

Naegeli¹⁵ explains the presence of the myeloblasts in Herxheimer's case as a compensatory activity of the stem cells of the leukocytes, following their oppression in the bone marrow. Similar observations have been cited by Fischer and Naegeli in lymphatic leukemia and in toxic anemia.

Ziegler⁴⁰ in his discussion of lymphatic and myelogenous leukemia states that an atrophy of one system means the hypertrophy of the other and vice versa. He says there must be a proliferation of the entire preformed tissue. But the fact that we have localized changes in leukemia speaks against Ziegler.

Hertz⁴¹ has shown in his experiments on animals that leukocytic metaplasia may occur without formation of red blood cells, and that formation of leukocytes and the erythrocytes do not always run parallel. These experiments would indicate that myeloid metaplasia is not merely a compensatory phenomena on the part of nature.

The fact that there was so much evidence of activity of both systems in my case at all times, even though one or the other predominated slightly during the course of the disease, would make it seem illogical to explain the condition on the compensatory basis.

The use of roentgen ray and drugs in the treatment of some of the previously reported cases of mixed leukemia have been urged as an explanation by men who object to this diagnosis. Since my case received no roentgen-ray treatment and was given no medicine except simple tonics, it will not be necessary to discuss this objection.

The explanation of the findings in true mixed leukemia is so closely correlated with the origin of blood cells that a discussion of the former subject would be very incomplete without mentioning, at least briefly, the theories and views on the latter subject. Ehrlich⁴² was the first one to lay down the laws of morphologic, biologic and genetic specificity of the white blood cells, namely, that lymphocytes originate in the lymphatic organs (spleen, lymph glands and adenoid tissue of the digestive tract) and the granular leukocytes along with red blood cells from the bone marrow. It has been shown since the time of Ehrlich that normal adipose tissue of the adult bone marrow can take on its embryologic function under pathologic conditions. Why, then, cannot the adult spleen which is rich in myelogenetic tissue in intra-uterine life, assume its myelogenous function again under a similar pathologic condition?

40 Ziegler, R. Experimentelle u klinische Untersuchungen über die Histogenese der myeloiden Leukämie, Jena, G. Fischer, 1906.

41 Hertz, R. Zur Frage der experimentellen myeloischen, Milz Metaplasie, Ztschr f klin Med 71:435, 1910.

42 Ehrlich, P., and Lazarus, A. (Rewritten by A. Lazarus and O. Naegeli, and translated by H. Armit) Anemia, New York Rebman Company, 1910, p 148.

Many clinicians and hematologists have discussed and tried to solve this question

Hematologists are divided into two great schools, the dualists on one hand, who believe that there is a specific separate stem cell for the lymphocytes and the myelocytes, and, on the other hand, the monophyletists, who believe that, at least under certain conditions, lymphocytes and myelocytes may have a common "mother" or "stem" cell

Among the chief exponents of the unitarian theory (monophyletic) as quoted by Downey and Fineman,³² are Pappenheim,⁴³ Grawitz,⁴⁴ Weidenreich,⁴⁵ Maximow, Downey,⁴⁵ Ferrata, Du Toit, Arnold, Neumann, and Danchakoff.⁴⁶ Among the chief exponents of the dualists are Naegeli, Ehrlich, Stockard, Ziegler, Turk, Schridde, Fischer, Butterfield, Stillman, Meyer and Heineke.

Ehrlich's classification of blood cells forms the basis of the modern dualistic teachings and is practically accepted by the great majority of the clinicians today. I will first mention some of the points which the dualists offer in favor of their theory.

Ehrlich and the dualists insist that there is a marked contrast between myeloid and lymphatic tissues in their origin. They believe it is impossible to have a mixture of myeloid and lymphoid metaplasia, and that the lymphoblast and myeloblast are very different in appearance and can always be distinguished from one another.

Fabian, Naegeli and Schatilloff,⁶ after an intensive study of many cases of lymphatic and myeloid leukemia, state that in no case did the lymphatic tissue become myeloid or vice versa. The findings in the organs as well as in the blood smears always showed the two types as distinct and separate.

Naegeli points to Herxheimer's case of apparent mixed leukemia as definite proof of the dualistic idea, in that here Herxheimer found a sharp distinction between the lymphocytic and myelocytic infiltrations in the different sections of the mediastinal tumor and the other organs studied.

Of course, as stated before, Naegeli⁷ insists that there are no transitions between the myeloid and lymphatic systems. He explains the presence of myeloid metaplasia in the spleen and lymph nodes and the action of myeloid elements in the blood, by dividing the tissues of the spleen into myeloid and lymphoid elements. He classified the

43 Pappenheim, A. Die Zellen der leukämischen myelose, Jena, G. Fischer, 1914.

44 Grawitz, E. Klinische Pathologie des Blutes, Leipzig, Georg Thieme, 1911.

45 Downey, H., and Weidenreich, F. Ueber die Bildung der Lymphocyten in Lymphdrusen und Milz, Arch f mikr Anat 80 367, 1912.

46 Danchakoff, V. Origin of the Blood Cells, Anat Record 10 397, 1916, Concerning the Conception of Potentialities in the Embryonic Cells, ibid 10 415 1916.

follicles of lymph nodes and spleen as being lymphoid, but the interfollicular tissue and pulp as being capable of producing myeloid cells

Schriddé⁴⁷ assumes that the endothelium of lymph vessels may give rise to lymphocytes, and that of blood vessels to myeloid tissue. However, Downey⁴⁸ has shown that lymphocytes are developed in great numbers in the spleen where there are no lymph vessels.

Naegeli,⁷ in his latest textbook, still insists that there have been no proven cases where the transition from lymphoblasts to myeloblasts has ever occurred.

Referring to the large, indifferent nongranular cells, Butterfield³⁹ believes that one cannot tell whether they are myeloid or lymphoid in origin, but he adds that they must be different because of the widely separated localization in the tissues of the myeloid and lymphoid elements.

MacCallum³³ states that lymphoid and myeloid tissues are so specific that they are never mixed. He insists that examples of abnormal metaplasia are due to transplantation of cells which then grow in their new locations.

The unitarians also have evidence for their theory. Pappenheim,⁴⁹ in 1908, assumed a common stem cell for both lymphocytes and myelocytes and says it is ubiquitous in all hematopoietic tissue. It may be the germ center cell of lymphatic tissue or the primary stem cell of myelogenous tissue. The presence of these stem cells may explain the origin of myeloid metaplasia of the splenic pulp and lymphoid metaplasia of the bone marrow. From them, by proliferation and differentiation, we may get lymphocytes or myelocytes, lymphatic or myeloid tissue, depending on whether the irritation is lymph or myeloplastic.

Pappenheim,²⁶ in a study of two cases of acute large cell leukemia, states that both cases point to the morphologic type of large lymphocyte of Ehrlich as an indifferent multipotent lymphoblastic and myeloblastic stem cell. Pappenheim concludes that, if the dualists are right, the large lymphocyte found in the first case can only be the stem cell of the myeloblast, and in the second case with many small lymphocytes, there must be a mixed leukemia, that is, a myeloidlymphadenoid leukemia, and in the former case a lymphadenoidmyeloid leukemia. They believe that in one case there is atrophy of lymphadenoid tissue and in the other suppression of myeloid production.

47 Schridde, H. Die embryonale Blutbildung, Erwiderung an Herrn Prof A Maximow, Zentralbl f allg Path u Path Anat **20** 433, 1909

48 Downey, H. On the Development of Lymphocytes in Lymph Nodes and Spleen, Tr Minn Pathol Soc 1912, 1914

49 Pappenheim, A., and Hirschfeld, H. Ueber akute myeloide und lymphadenoide, makrolymphocytare Leukämie an der Hand von zwei verschiedenem Fällen, Folia Haematol **5** 347, 1908

Citron,³¹ in 1915, reported a case of leukemia where the blood showed a definite myelogenous picture with a normal bone marrow. Citron's conclusion was that the micromyeloblastic cells of the blood were being generated in the follicles and interfollicular tissue of the lymph nodes and spleen, and that these cells were passing from the follicles into the blood stream.

Fineman³² presented a case of acute micromyeloblastic leukemia where a lymph node was obtained *in vivo*, the study of which showed 'atypical cells proliferating in great numbers in the capsule, interfollicular tissue, lymph cords, lymph follicles, and in the germ centers of the lymph follicles. Transition forms between the connective tissue cells of the capsule and these atypical cells, as well as between lymphocytes and the atypical cells, were present in the capsule. In the interfollicular tissue, as well as in the follicles, and even in the germinal centers, transition forms between these atypical cells and reticulum and lymphocytes were also present. These atypical cells form the majority of the cells of the parenchyma.' In conclusion, he states that the myeloblasts and micromyeloblasts of the blood were coming from these atypical cells found in the organs.

These two cases (Citron and Fineman) are of utmost significance, in that they are the first ones on record which would seem to prove that the dualistic doctrine of the origin of white blood cells does not always hold true.

Werzberg,²⁵ in studies on myeloid metaplasia, found in his cases all transitional stages from the large lymphocyte to the fully differentiated polymorphonuclear cell. He found intensive hyperplasia of splenic follicles with rarefaction of splenic pulp which was undergoing myeloid metaplasia. The large lymphocytes of the bone marrow were identical in structure with those of the germ centers and the pulp of the spleen.

Downey's⁴⁸ investigations show clearly that the lymphocyte is not a fixed and fully differentiated cell which is incapable of further differentiation, as was claimed by Ehrlich. He has seen it develop into a large mononuclear macrophage as well as into plasma or mast cells. He states that the lymphocyte is really a primitive, rather indifferent cell whose morphologic appearance depends on the stage of development and the particular function which it happens to be performing at the time. It is capable of differentiating into various types of granular leukocytes. Downey does not recognize the term "lymphoblast" used so much by Naegeli in his description of the large mononuclear cell of the germ centers. The large lymphocytes of the germ centers which Downey studied, did not conform to the description given by Naegeli and others. Downey has shown that there is not a particular type of lymphocyte only found in the germ centers, but that the same cell

occurs also in the interfollicular tissue or in the splenic pulp, in fact, everywhere in the adenoid tissue, and that the lymphocytes have a twofold origin, namely, from the reticulum, and from large mononuclears which came from the reticulum, or from lymphocytes.

In spite of the apparent antagonistic views of the unitarians and dualists, concessions have been made on both sides. Naegeli, in the last edition of his textbook, admits that the mesenchyme cell found in the neighborhood of the blood vessels may differentiate under pathologic and physiologic conditions in both directions. In this respect, at least, he is a unitarian. On the other hand, Pappenheim⁹ stated that at present a morphologic difference between lymphatic and myelogenous lymphoid cells must be admitted, although it has not been proved definitely that development cannot occur from one to the other, or that a myeloid cell in the blood must always be derived from myeloid tissue and a lymphocyte from lymphatic tissue.

The formation of lymphocytes from myeloid tissue can be explained by the dualists on the basis of substitution.

Some men hold an intermediate view between the unitarian and dualistic. Hirschfeld⁵⁰ believes the "golden" middle position between the dualistic of Ehrlich and the absolute unitarian ideas of younger authors to be the best. The stem cells of the lymphatic and myeloid tissues are morphologically the same but are different in their function and further cytologic differentiation.

Browning¹⁶ believes leukemia to be a sarcoma of the blood with reversion to the embryonic type of cell, that is, reversion to the condition existing in the marrow of fetal life. The case which he gives as an example has already been discussed. As to the origin of blood cells, his observations on the findings in the human fetus indicate that eosinophilic and neutrophilic leukocytes arise from the mitotic division of large mononuclear granular cells lying in the loose connective tissue. Large nongranular basophil cells are the result of reversion of granular myelocytes to the nongranular "premyelocyte" or leukoblast or so-called "stem" cell stage. He states that Muir agrees with him.

Danchakoff⁴⁶ believes that the stem cell, or so-called large lymphocyte appears first during the dissociation of the blood islands and is a young undifferentiated cell which differentiates according to given environmental conditions. She states that the fact that stem cells, as stem cells, keep their morphologic structure so tenaciously under the most varied condition, and that only their products differ, seems to speak strongly for the existence of a single cell identical in the hematopoietic organs.

⁵⁰ Hirschfeld, H. Die unitarische und die dualistische Auffassung über die Histopathologie der Leukämien, *Folia Haematol* 6: 382, 1908.

Observations in my own case point toward the unitarian idea as being the correct one for the following reasons First, that from a study of the blood smear there seems to be a common stem cell for developing lymphoid and myeloid cells, as a series of both types could be found, starting with this apparently common stem cell Second, this same common stem cell could be found in the tissues in the spleen, lymph nodes, kidney, lungs and pancreas mixed in with developing myeloid and lymphoid cells Third, that many of the young eosinophilic myelocytes as well as the adult eosinophils had nuclei which were identical with adjacent lymphocytes These myelocytes were not the type found in normal marrow It seems logical to deduct that they differentiated directly from the small lymphocyte Some of the granules of the young eosinophils were still very young, indicated by their basophilic staining Fourth, that differentiating lymphocytes and myelocytes were found diffusely intermixed in the tissues away from the neighborhood of blood vessels in most of the organs studied

The above findings, in my opinion, could not be as satisfactorily explained on any other theory except that held by the unitarians

Again, if there is a separate stem cell for the myelocytes as Naegeli claims, I should have found more myelocytes in the areas of cell infiltration in the liver If the so-called "stem" cells which were present are myeloblasts as Naegeli would call them, why do I not find more myelocytes here as I did elsewhere? It is evident that the dualistic theory cannot explain the condition found in the liver satisfactorily in correlation with the findings in the other organs

In concluding the discussion of the subject of mixed leukemia, I should like briefly to compare my case with those previously reported The blood findings apparently resemble that found by Turk in his first case In both cases the myeloid element predominated primarily, while later lymphoid activity was slightly more pronounced This is also true of Wilkinson's case

Hirschfeld² found myeloid metaplasia in the splenic pulp and lymph glands, along with lymphadenoid metaplasia in the bone marrow He showed a continuous series of transitional forms leading from the typical acute lymphocytic leukemia to the acute mixed cell type, such as were seen in my case

In the cases of Herxheimer and Herz, the lymphatic hyperplasia was primary, with the myeloid activity developing later Herz's observations of the myeloid changes in the spleen and lymph nodes were similar to my case, except that there seemed to be more of a separation between the two types in the case of Herz, while mine, as mentioned before, showed a diffuse mixture of the two

Herxheimer also emphasized the fact that there seemed to be a distinct separation of the areas of myeloid and lymphoid activity and

therefore called his case one of combined lymphatic and myeloid leukemia rather than a true mixed type.

The cases of Hirschfeld and my own seem to be the only ones reported in the literature which show histologic study to support the blood findings in making the diagnosis of true mixed leukemia.

Before concluding this paper, I wish to correlate some of the more important ideas regarding mixed leukemia, and discuss very briefly the subject itself. I have already discussed the objections which certain hematologists make against the diagnosis of true mixed leukemia, so I will limit myself now especially to the reasons why some hematologists believe it is possible that a form of true mixed leukemia can exist.

Let me repeat again the requirements which von Domarus and Browning have stated are necessary in order to make the above diagnosis, namely, that one must find in the histologic preparations hyperplasia of both myeloid and lymphatic tissue next to each other and occurring at the same time. Von Domarus quotes Hirschfeld's case as the only one of true mixed leukemia that has been reported. However, at the time when this statement was made, Herxheimer's case had not appeared in the literature.

The various men who have reported cases which they believe to be true combined or mixed leukemia, explain the cause of the simultaneous activity of the two systems in many ways.

Browning feels that the mixed cell picture is due, first, to the reversion of the myeloid cells to the embryonic nongranular type, second, a reaction or mechanical disturbance of the myeloid tissue, owing to lymphoid hyperplasia, resulting in the passage of myelocytes into the circulation. He feels that the toxins causing leukemia vary in their action and may give mixed types. However, he carefully avoids making any statement as to whether he believes his case to be one of true mixed leukemia.

Hirschfeld felt that the fact that his case showed undisputable evidence of simultaneous activity of both systems was enough evidence on which to make a diagnosis of mixed leukemia. He offers no opinions as to how the mixed cell picture is brought about.

Herz calls his case one of mixed leukemia, yet he states in his discussion that the hyperplasia of the lymphadenoid tissue within the myeloid bone marrow, and the hyperplasia of the lymph follicles and pulp strands in the lymph glands, to the complete loss of structure, does not necessarily signify an exceptional increase of the lymphadenoid tissue components of a myeloid leukemia, but is a disease of the lymphatic system itself along with a similar disease of the myeloid tissue, that is, a lymphatic leukemia with a myeloid leukemia. In another place he says, "the fact that, along with many lymphocytes, an important

number of the elements of the myeloid tissue were present in the blood proves there must be a disease of both types of tissue, that is, a mixed leukemia." He suggests that the same poison or toxin may act on the one tissue and later on the other, or there may be two different toxins, and further that the infectious toxic agent may cause a reaction of both tissues at the same time, or after an exhaustion of one system, call forth an activity of the other. I cannot tell whether Herz believes his case to be one of combined or mixed leukemia, that is, whether he makes a distinction between the two words.

Herxheimer, however, leaves no doubt in one's mind in regard to his belief that his case is one of a combined leukemia, that is, an activity of both the lymphatic and myeloid systems with a distinct separation of the two types throughout. He emphasizes this fact in the discussion of his case, stating that nowhere was there evidence of fusion of myeloid and lymphoid elements. He believes this observation to be a strong point in favor of the dualistic theory, and cites his case as a good example of one showing that the two forms of leukemia can go on together and yet be distinct. I believe that both Herz and Herxheimer are dualists at heart. Herxheimer concludes that his case speaks against any transitional forms between the two types of cells, and says that the second one can only exist in the sense of a combination like carcinoma and sarcoma in the same individual without carcinomatous cells changing into sarcomatous cell.

In regard to my own case, as well as those before mentioned, it is evident that it meets all the requirements laid down by von Domarus and Browning in order to be called true mixed leukemia. It differs from the cases of Herz and Herxheimer in that I found a definite fusion and mixture of both systems, most marked in the spleen, lymph glands, alveolar walls of the lungs, interacinar tissue of the pancreas and in the kidneys. Although the presence of the myelocytes in the extramedullary organs may be explained on the bases of de-differentiation of the lymphocytes back to the stem cells and then to the myelocytes, it seems that there is more evidence of a direct formation of myelocytes from lymphocytes as has already been discussed in detail. It is important to note again that these myelocytes were present in the interfollicular tissue, not just around the blood vessels where Naegeli believes that they are only found. It is evident that the findings in Hirschfeld's case, and my own, speak very strongly against the dualistic theory of Ehrlich and his followers, and favors the unitarian idea in the sense that there is apparently a common stem cell for both types of developing cells. But also in my case there is evidence of a direct transition from lymphocytes to myelocytes without going through the stage of the stem cell.

As to the cause of the picture of mixed leukemia, I probably can offer no new suggestions, at least no better than have already been given. The fact that there may be two toxins present, one stimulating the lymphatic system, the other stimulating the myeloid system, is possible, but it seems more likely, at least in my case, that there was only one toxin which excited an abnormal activity of both systems, because of the fusion of the products of activity of the two systems.

It is possible that there may be only one kind of acute leukemia, at least in a hemomorphologic sense, and that the lymphoid cells of acute lymphatic and myeloid leukemia are isomorphic. No evidence has been given, however, to confirm this idea.

Weizberg²⁵ believes that leukemia, as a whole, is after all, a true endogenous disease whose direct cause is not one of a common excitant or mysterious poison, but a one sided cellular disturbance that attacks the normal organs.

I do not believe we will find the explanation of true mixed leukemia until we determine the cause of simple leukemia. The question must still remain open with a hope that future investigations may give us more definite information on this peculiar malady of mankind.

SUMMARY

1 Report of a case of acute leukemia, showing definite evidence in the blood smears as well as in the histologic study of the tissues of activity of both the myeloid and lymphoid systems.

2 Cells representing the various stages in the development of lymphocytes and granular leukocytes from the original "mother" or "stem" cell to the adult types could be found in the blood smears.

3 Immature lymphocytes and myelocytes were found mixed together in the pancreas, kidneys and lung in the areas of leukemic infiltration.

4 Myeloid and lymphoid metaplasia was noted in the spleen and lymph nodes, with a slight predominance of the latter. Immature cells of both types were diffusely arranged with no evidence of segregation.

5 There was evidence of local development of myelocytes from lymphocytes in the tissues.

6 Many of the immature myelocytes, particularly the "stem" cells, showed the typical coarse "myeloid azurite granulation of Pappenheim."

7 Histologic studies showed a similar, simultaneous hyperplasia of lymphatic and myeloid tissue next to each other, which are the necessary findings required by von Domarus and Browning, in order to give it the name of the true mixed leukemia.

8 There was no evidence of sepsis found at necropsy.

9 There was apparently a single toxin stimulating both systems into a leukemic activity.

10 The findings in the blood smears, as well as in the histologic study of the organs, pointed to the unitarian theory of the origin of blood cells as being the correct one, at least in certain pathologic conditions

11 No new observations were made relative to the real cause of the simple or mixed form of leukemia

12 Another case of a true mixed form of leukemia is added to a small number of previously reported cases

Sivertsen Clinic, 2319 Sixth Street, South

A HITHERTO UNDESCRIBED FORM OF VALVULAR AND MURAL ENDOCARDITIS*

EMANUEL LIBMAN M D

AND

BENJAMIN SACKS M D

NEW YORK

In previous communications¹ cases of endocarditis were classified as rheumatic syphilitic bacterial—acute and subacute—and indeterminate. The latter term was introduced to designate certain cases which do not fall into the category of any of the well-recognized groups of endocarditis and the etiology of which is not yet established. The term is used to include (a) the cases of so-called terminal or cachectic endocarditis occurring at the close of chronic diseases such as carcinoma, tuberculosis, nephritis and leukemia and (b) cases of atypical verrucous endocarditis. The purpose of the present communication is to discuss the cases included in the latter group which we believe represent a hitherto undescribed form of endocarditis.

We are at the present time reporting the study of four cases clinical observations of which were supplemented by postmortem examinations. In each instance there were peculiar valvular and mural lesions which differed in morphology and localization from those generally encountered in subacute bacterial rheumatic and other forms of endocarditis. The vegetations were free from demonstrable micro-organisms and attempts to grow bacteria from the blood proved unsuccessful despite the employment of methods which gave positive results in the great majority of cases of subacute anhemolytic streptococcus (and *Bacillus influenzae*) endocarditis. Because of the unusual character of the endocardial lesions and their verrucous appearance these cases were designated atypical verrucous endocarditis. When this form of endocarditis is better understood a more satisfactory terminology will doubtless be introduced.

REPORT OF CASES

CASE 1—History.—S. H., a woman married aged 24, admitted to the Mount Sinai Hospital Jan 21 1922 and whose family history was unimportant three years prior to admission to the hospital had an attack of polyarthritis during which her ankles, knees, wrists and elbows became painful and swollen. She states that she lost 60 pounds (27.2 kg.) during 1921.

* Read in abstract before the Association of American Physicians Atlantic City N. J. May 1 1923

* From the Medical and Pathological Departments Mount Sinai Hospital
1 Libman Emanuel Characterization of Various Forms of Endocarditis,
J. A. M. A. 80:813 (March 24) 1923 Brit. M. J. 2:304 (Aug 28) 1920

Her general health was good until six weeks before admission, when she developed "sticking" precordial pain which was intensified on deep inspiration. Two weeks later, she had a chill, followed by fever, and her ankles, knees, wrists, elbows and shoulder joints became swollen and tender. At the same time, her face became greatly swollen, and the urine was scanty. She experienced "drawing" pains in the left lumbar region, and the blood pressure was elevated. A week before admission, she developed sore throat. The edema of the face diminished, but the articular and precordial pains persisted.

Physical Examination.—The patient was poorly nourished and acutely ill, and had a temperature of 103.4 F. There were present slight puffiness and pallor of the face. Petechiae were present in the conjunctival mucous membrane of both lower lids and on the anterior aspect of the thorax and both sides of the neck. The pupils were equal and reacted promptly to light. The tonsils were moderately enlarged and congested. The respirations were shallow and somewhat accelerated, but not labored. The lungs were negative. The heart was not enlarged, the action was rapid but regular. The first sound at the apex was increased in intensity. A systolic murmur was audible over the entire precordium and in the left axilla. The second pulmonic sound was accentuated. The pulse rate was 96, respiration rate 36, and the blood pressure, 145 systolic, 90 diastolic. The abdomen was distended and held rigidly, and there were pain and tenderness in the left hypochondrium. Neither the liver nor the spleen was palpable. The left elbow and both ankle joints were swollen and tender, but the overlying skin was not reddened. The right elbow joint, both wrist joints and the left knee joint were tender, but there was neither swelling nor redness. Over the extensor surface of both forearms, the skin showed erythema and induration, and there was both cutaneous and muscular tenderness (dermatomyositis). The deep and superficial reflexes were active.

Course.—January 23 The pulse was 120, respiration, 44. The petechiae were fading. The urine was reduced in quantity and contained a heavy trace of albumin and a few hyaline casts. The blood showed no nitrogen retention (compare figures below).

January 24 Over the ramus of the left mandible, there was a distinct white-centered petechia. The patient had been having frequent attacks of pain in the left hypochondrium.

January 25 The fundi were normal.

January 27 The dermatomyositis had disappeared.

January 29 Both elbow joints were tender. There were dulness and diminished breathing at the left base posteriorly, below the level of the angle of the scapula.

January 30 The joint pains had improved.

February 4 The first to the fourth left metacarpophalangeal joints, inclusive, were painful and tender, but although there was practically no periarticular swelling, the skin overlying the dorsal aspect of the joints was of a peculiar red color, unlike that seen over the seat of typical rheumatic arthritis.

February 7 There was now dulness and diminished breathing over both lower lobes, posteriorly.

February 8 The pulse was 116, respiration, 28. A to-and-fro pericardial friction rub was audible in the region of the apex of the heart and over the left fourth interspace just lateral to the sternum. The patient complained of "sticking" precordial pain similar to that experienced at the onset of her illness.

February 14 The friction rub had disappeared. Diffuse moist râles were audible over both lungs and there was profuse seromucoid expectoration.

February 17 The precordial pain, which had disappeared for a time, returned. The temperature rose to 104 F., and the pulse rate to 140.

February 19 Thoracentesis on the right side yielded 250 c.c. of clear fluid and on the left side 20 c.c. of blood-tinged fluid. The fluid from both sides was sterile. The general condition of the patient was growing progressively worse.

February 21 A fresh crop of white-centered petechiae appeared over both sides of the neck and on the anterior aspect of the chest. The temperature dropped to 93.8 F, but the pulse rate remained accelerated, and was now 120.

February 22 The neck was rigid, and the Kernig sign was positive, bilaterally. Chemical examination of the blood now showed definite nitrogen retention. Blood cultures were persistently negative.

March 1 The abdomen showed signs of fluid and both lower extremities were edematous.

March 5 Numerous fresh petechiae appeared in the palpebral conjunctiva and on the skin of the neck and thorax.

March 7 There was a small exudate in the fundus of the right eye on the nasal side of the disk.

March 10 A bed sore appeared over the sacrum. There were signs of bilateral pleural effusion and ascites. The lower extremities and vulva were greatly swollen.

March 13 The patient had been having attacks of severe precordial pain radiating to the back and left shoulder. A few fresh petechiae had appeared in the left lower palpebral conjunctiva. The temperature for the last two weeks ranged around 100.

March 19 The patient began to vomit bloody fluid.

March 22 The breathing was labored and the breath uremic. Albuminuria became more marked. Paracentesis abdominis yielded 1,500 cc of clear straw-colored fluid.

March 24 A fresh crop of petechiae appeared.

March 31 Ascites and edema were increasing. Paracentesis was performed. The daily urinary output varied between 300 and 600 cc. The precordial pain persisted and morphin was frequently required for its relief.

April 4 The patient had a generalized convulsion, following which she remained comatose for some time. When consciousness returned, she complained of severe precordial pain.

April 6 A second convulsion, ushered in by pain in the right arm, was followed by pulmonary edema.

April 13 Paracentesis abdominis yielded 5 liters of clear straw-colored fluid.

April 29 The ascitic effusion reaccumulated and the subcutaneous edema spread to the abdominal wall. A new crop of petechiae and purpuric spots was present.

May 3 A diffuse herpetic eruption (herpes zoster) appeared on the left side just below the breast and the angle of the scapula. The edema now became generalized. The precordial friction rub was again audible.

May 23 The pulse rate varied between 80 and 100. No new murmurs appeared. From time to time, the patient complained of severe epigastric and precordial pain.

May 29 The oliguria became more marked, and the general condition was growing progressively worse.

May 31 The patient suddenly became dyspneic and cyanotic, with pulse more rapid and irregular. She grew stuporous and died.

Temperature Curve—January 21 The range was from 101 to 103.6 F.

January 22-27 The temperature gradually came down in remittent fashion to 101.2 F.

January 28-February 3 The temperature was not over 101 F at any time. At the end of the week, it was down to 99.6 F.

February 4-10 The temperature was irregular, remittent and gradually higher until it reached 103.8 F, February 10.

February 11-17 The temperature was irregular, ranging from as low as 99.6 F, to as high as 104 F (February 17)

February 18 The temperature ranged from 100 to 104.4 F

February 19 The temperature remained near 104 F

February 20 There was a sharp drop to 98 F

February 21-25 The temperature was irregular, ranging from 97.2 and 98 to 100 and 101 F

February 26-27 The temperature was 101 F

February 28-March 23 The temperature was never above 100.4 F, usually at 99 or 100 F

March 24 The range was from 99 to 101.8 F

March 25-April 5 The temperature was never over 101 F, and was sometimes as low as 97 F

April 6-14 The temperature was not over 99 F, excepting for a rise on the last day to 100.6 F

April 15-May 3 The temperature was very low, never over 99.8 F, often 98 F

May 4-May 31 At times, the temperature was as low as 96.4 F or 97 F, usually not over 99 F, except for a rise to 100.6 F, May 4, and 101 F, May 21

Respiration—January 21-31, the rate was usually about 36. Later, it varied from 24 to 28, occasionally rising to 32 or 36. After February 18, it increased to 40, remaining near that figure until after March 18, when it dropped to a figure usually varying between 24 and 28, sometimes dropping as low as 20.

Pulse Rate—January 21-27, the rate was usually 120. It gradually decreased, and after February 1, it ranged from 84 to 100. With sharp rises of temperature, it increased, reaching as high as 142, February 19, and 154, February 20. After February 26, it was usually 110-132, even though the temperature did not rise above 101 F.

Amounts of Urine—At first, the figures varied between 700 and 2,200 cc, after February 11, from 600 to 750 cc. The amount remained about the same after this time, at times increasing to 900 cc, or decreasing to 300 or even 115 cc. After March 25, the amount never exceeded 625, and often was as low as 250 or 150 cc.

Laboratory Examinations—These are given in Table 1.

Necropsy (eighteen hours after death)—The body was that of a well developed, emaciated young woman, showing marked pallor of the skin and mucous membranes. No petechiae were present. There was marked pitting edema of both lower extremities extending as far as the calves. There were several decubitus ulcers, the largest of which was 30 cm in diameter. The base of the ulcers was covered with a dirty greenish exudate. The skin over the left fifth and sixth intercostal spaces both anteriorly and posteriorly showed desquamation and pigmentation (residue of recent herpes zoster).

The heart was moderately enlarged, weighing 360 gm. The pericardial membranes were universally thickened as a result of organizing fibrinous pericarditis, and there were extensive friable adhesions between the visceral and parietal layers, which almost completely obliterated the pericardial sac. The adhesions over the anterior aspect of the left ventricle were quite fibrous and were firmer than elsewhere. There was no effusion. There were rather firm, fibrous adhesions binding the parietal layer of the pericardium to the adjacent pleura on the left side. The tricuspid valve showed a discontinuous fibrous thickening representing a healed organic lesion. There were several minute healing translucent vegetations along the line of closure. The pulmonary valve was negative. The mitral orifice admitted three finger tips. The mitral valve showed a fairly continuous fibrous thickening involving the closure line and free

edge, pointing to a previous attack of endocarditis. Along the line of closure, extending in places to the free edge, there was a row of rather firm translucent grayish verrucous vegetations (Fig 1). A part of some of these was yellowish gray in color and opaque.

The endocardium over the upper part of both papillary muscles of the left ventricle and the intervening mural endocardium was the seat of an inflammatory process. There had also been an extension of the endocarditic process from the

TABLE 1.—*Laboratory Examinations*

Urine							
Date	Amount, Cc	Appearance	Reaction	Specific Gravity	Albu- min	Sug <i>n</i> l	Microscopic
1/22		Cloudy	Acid	1.018	++	0	Hyaline casts no erythrocytes
2/27		Cloudy	Alkaline	1.020	++	0	Numerous leukocytes and a few erythrocytes
3/10	400	Cloudy	Alkaline	1.022	+	0	Numerous leukocytes and erythrocytes, and a few granular casts
4/11	350	Cloudy	Alkaline	1.014	++++	0	A few erythrocytes
4/19	400	Cloudy	Alkaline	1.012	++++	0	A few leukocytes and hyaline casts, no erythrocytes
5/22		Alkaline		1.020	+++	0	Hyaline and granular casts numerous erythrocytes
5/29		Turbid	Alkaline	1.010	++	0	Numerous erythrocytes and leukocytes
Blood Chemistry							
Date		Urea N, Mg per Hundred	Nonprotein N, Mg per Hundred	Uric Acid, Mg per Hundred	Creatinin, Mg per Hundred		
		Cc	Cc				
1/23		22.4	46.7	5.0	2.0		
2/17		25.2	50.9	3.3	1.4		
2/22		64.4	104.2	4.2	2.8		
4/24		49.0	71.6				
Phenolsulphonephthalein Test (1 Cc Injected)							
1/24				50 per cent recovered in 2 hours			
1/25				45 per cent recovered in 2 hours			
3/20				30 per cent recovered in 2 hours			
4/2				5 per cent recovered in 2 hours			
Blood Count							
		Date					
		1/22	2/12	3/6	3/31	4/29	
Red blood cells		5,400,000	2,936,000	2,088,000			2,500,000
Hemoglobin, per cent		84	56	34	39		38
Color index		0.86	0.96	0.83			0.76
White blood cells		6,500	5,400	13,400			21,600
Polymorphonuclear neutrophils, per cent		84.0	67.5	79.0			72
Eosinophils, per cent		1.0	2.0	0.5			0
Basophils, per cent		0	1.0	0.5			1
Lymphocytes, per cent		13.0	23.0	19.0			25
Monocytes, per cent		2.0	5.5	1.0			2
Neutrophilic myelocytes, per cent		0	0.5	0			0
Plasma cells, per cent		0	0.5	0			0
Platelets				192,000			
Coagulation time				12 min			
Bleeding time				2 min			
Capillary resistance test				4 min			
Clot retraction				Neg			
				Present			
				Present			

* The Wassermann reaction of the blood was negative. Blood cultures were made four times (January 22 and 28, and February 1 and 22), the mediums used were bouillon and glucose bouillon flasks, and plain agar and glucose agar plates, all were negative.

ventricular aspect of the posterior cusp of the mitral valve downward along the mural endocardium of the ventricle toward the tip of the posterior papillary muscle. The surface in these areas was covered by extensive flat grayish brown and yellowish patches of firm but friable deposit. The lesions on the mural endocardium just lateral to the posterior papillary muscle were grayish and more fibrous than elsewhere. Near the apex of the left ventricle, there was a

flat area of mural endocarditis, measuring 25 by 30 cm, irregular in outline and sharply demarcated from the surrounding healthy endocardium (Fig 1). The patch presented a lusterless irregularly fissured surface, which was a mottled, grayish and reddish brown. On cut section, the deeper layers had a grayish translucent appearance, and delicate fibrous strands extended into the subjacent myocardium. The aortic valve showed a few minute firm translucent vegetations. The myocardium was pale and brownish, showing numerous fine grayish streaks. The coronary arteries and aorta showed a slight degree of atherosclerosis.

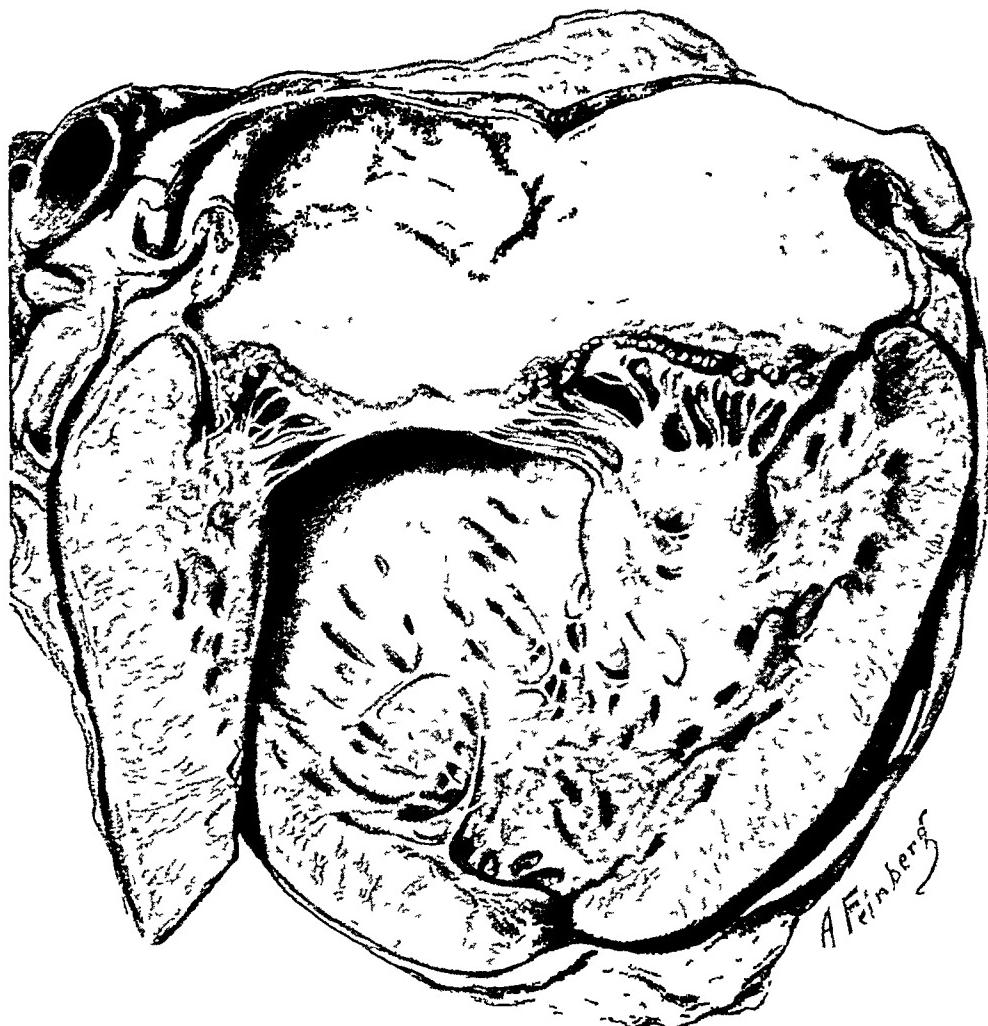


Fig 1 (Case 1)—Left side of heart. Verrucous vegetations along line of closure of mitral valve extending in places to the free edge. There are areas of endocarditis on papillary endocardium and adjacent mural endocardium and an isolated patch of mural endocarditis in region of apex of ventricle. Universal healing fibrinous pericarditis is present.

In the lungs, there were friable adhesions between the visceral and parietal pleura on both sides, especially marked in the region of the diaphragm. These adhesions were the result of the organizing exudate of recent fibrinous pleurisy. The left pleural cavity contained about 250 cc of clear fluid. There were numerous minute subpleural hemorrhages. Both lungs showed marked congestion and edema, but no areas of consolidation.

The abdomen was markedly distended, the umbilicus being flush with the surface. The peritoneal cavity contained 4 liters of clear yellowish ascitic fluid. There was no evidence of peritoneal inflammation.

The liver was shrunken, weighing 780 gm. The capsule was wrinkled and the parenchyma was pale, brownish and cloudy, and showed marked chronic congestion.

The spleen was small, weighing 80 gm. The organ was of a rather firm elastic consistency. The malpighian bodies were small and the pulp showed congestion. Near one of the poles was a small depression, which on cut section was found to be due to a healed infarct.

In the kidneys, the capsule of the right stripped with difficulty, revealing a granular and nodular surface. The elevated areas was a pinkish gray, whereas the depressed areas were a deep red. On cut section, the cortex was somewhat narrower than normally, having a thickness of from 0.4 to 0.5 mm. The cortical tissue was pale and turbid, a mottled pink and gray. These striations were indistinct, and the glomeruli were not prominent. The left kidney showed in addition to the changes seen in the right kidney, a number of abscesses in both cortex and medulla, their diameter varying from 0.3 to 1.5 cm. Cultures of the pus from the abscesses showed *Staphylococcus aureus*. The pelvis, ureters, bladder, uterus and adnexa were negative.

Microscopic Examination—Examination of the myocardium and pericardium revealed an organizing fibrinous pericarditis. The muscle fibers were atrophic and showed marked interstitial edema, and there were numerous small areas of interstitial fibrosis. There was no evidence of Aschoff bodies or Bracht-Waechter lesions.

Examination of the mitral valve and mural endocardium showed that the greater part of the vegetations on the mitral valve consisted of a mass of hyaline thrombus on which was deposited a fresh agglutinated blood platelet thrombus, the surface of which was only partially covered by endothelium. The patches of mural endocarditis showed extensive deposition of hyalinized blood platelet thrombus, the greater part of which was not clothed by endothelium. The endocarditic process had invaded the underlying myocardium rather deeply, with resulting destruction and replacement of many of the muscle fibers (Fig 2). The deeper layers of both the valvular and the mural lesions were diffusely infiltrated with round cells and showed extensive fibrosis, indicating healing. The patch of mural endocarditis adjacent to the anterior papillary muscles showed infiltration of the thrombotic deposit with calcium salts.

In the lungs there was organizing fibrinous pleurisy, congestion and edema.

The liver showed parenchymatous degeneration and chronic passive congestion. The central veins were somewhat thickened.

In the spleen, the malpighian bodies were hypoplastic and the pulp showed congestion of the venous sinuses. In the latter were numerous phagocytic cells, containing granules of greenish pigment. At one point, there was a small healed infarct just below the capsule.

In the kidneys, there was universal glomerular injury typical of subacute diffuse glomerulonephritis. The glomeruli showed obliteration of various loops with hyalinization and fibrosis, and adhesions to Bowman's capsule. Many of the glomeruli were completely obliterated. The tubules showed parenchymatous degeneration, and the medium sized arteries presented atherosclerotic thickening. The left kidney showed, in addition, cortical and medullary abscesses.

COMMENT

The outstanding features were the onset with precordial pain followed by glomerulonephritis, the protracted course with irregular fever and progressive anemia, cardiac murmurs, acute pericarditis,

the recurrent crops of white-centered petechiae, arthritides, the symptoms pointing to splenic infarction, nitrogen retention in the blood, anasarca, attacks of abdominal pain and hematemesis simulating Henoch's purpura, localized dermatomyositis, herpes zoster, and repeatedly negative blood cultures. The patient died in uremia. The clinical picture was unique, and it was difficult to arrive at a single diagnosis which satisfactorily explained all the symptoms. The loud widespread systolic murmur which was noted before the development of anemia, the peri-

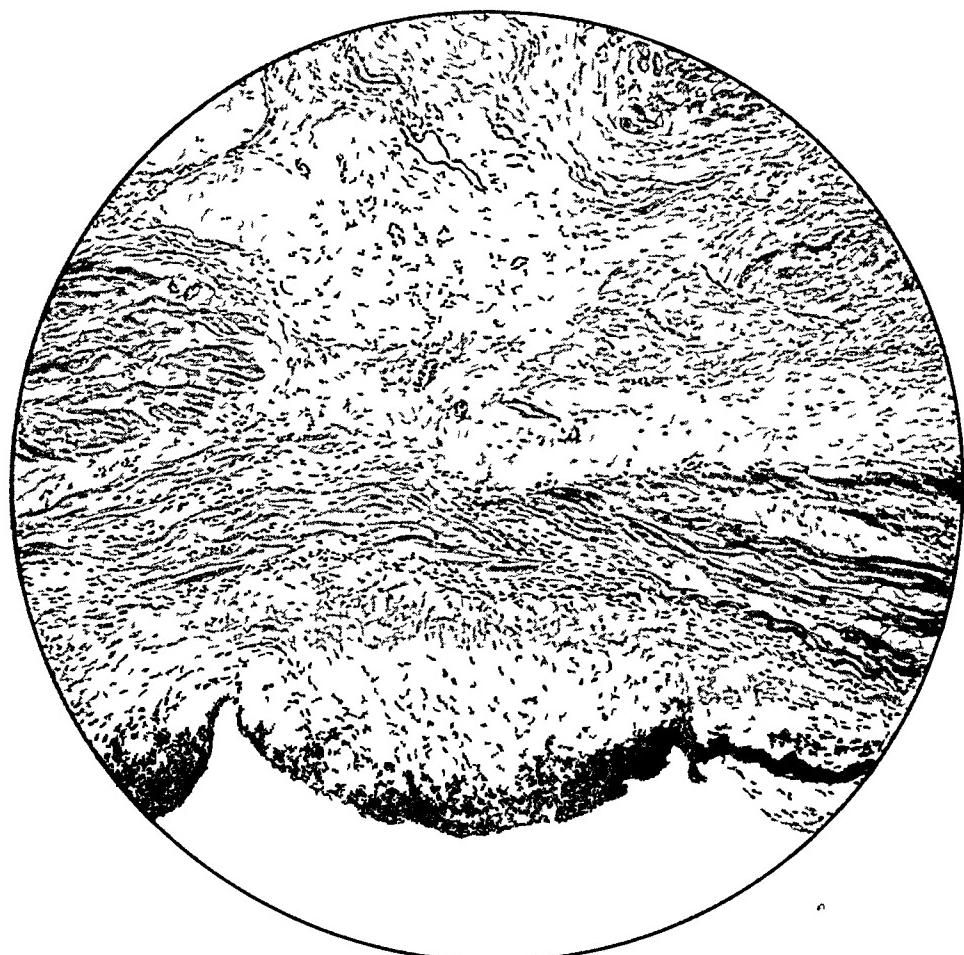


Fig. 2 (Case 1).—Microscopic section of apical patch of mural endocarditis. There is an extensive superficial deposition of hyalinized thrombotic material, not clothed by endothelium. Advanced fibrosis is present in subendocardial tissues, with destruction and replacement of many of the underlying muscle fibers. There are focal and diffuse areas of round-cell infiltration and vascularization in the deeper layers.

carditis, fever, tachycardia, which was marked even when the pyrexia was low, petechiae and embolic symptoms furnished ample evidence of the existence of some form of endocarditis, and the differential diagnosis appeared to lie between subacute bacterial and rheumatic endo-

carditis The white-centered petechiae, symptoms of splenic infarction and nephritis suggested the former diagnosis, whereas, the pericarditis and marked arthritis pointed toward the latter. On the other hand, white-centered petechiae do not appear in rheumatic endocarditis, and pericarditis is not observed in subacute bacterial endocarditis, except when there is diffuse glomerulonephritis with marked retention of nitrogen.

Because the clinical findings could not be explained by the presence of either form of endocarditis alone, it was concluded that the patient was possibly suffering from a combined infection due to the etiologic agents of both diseases. Had the blood cultures been positive, the diagnosis could have been ventured with greater assurance. Assuming the diagnosis to be correct, it was difficult to account for the occurrence of acute nephritis at the onset of the disease, and the dermatomyositis, the significance of which will be discussed later. Instead of a combined infection of the heart valves, the postmortem examination revealed the peculiar valvular and mural lesions which characterize the atypical form of endocarditis.

CASE 2—History—E. E., a woman, aged 37, admitted to the Mount Sinai Hospital, Jan. 25, 1923, gave an unimportant history. Nine months before entering the hospital, she developed painful swelling in both ankles. She had fever and was obliged to remain in bed for a time. Later, the pain spread to various other joints. Three weeks before admission, she suddenly developed chilly sensations, fever, sweats and cough. She was admitted to the hospital, complaining of shortness of breath, painful deglutition and sore throat, symptoms which she had developed during the previous night.

Physical Examination—The patient was well nourished. She was acutely ill, and had a temperature of 104.8 F. The respiration was labored and rapid, but there was no cyanosis. Over the bridge of the nose, extending symmetrically over both cheeks, was an erythematous eruption of butterfly pattern, resembling acute lupus erythematosus disseminatus. There were also patches of erythema over both elbows. The left third of the upper lip was slightly swollen. On the buccal mucosa of the lower lip was a small area of ulceration, 5 mm in length, covered by a grayish white membrane. On the dorsal surface of the left side of the tongue near the tip, there was a linear area of ulceration, 1 cm in length, which was covered by a finely adherent grayish membrane. The margins were dark red, and the surrounding mucosa was infiltrated and purplish. There was marked pyorrhea alveolaris. The pharynx and tonsils were congested, and the vocal cords were swollen and reddened. Below the level of the ninth dorsal spine on the left side, there were flatness and an absence of voice sounds. The breath sounds over this area were scarcely audible. The heart was not enlarged and the action was regular but rapid. The sounds were not altered in quality, and there were no murmurs. The free edge of the liver was felt 4 cm below the costal margin in the mammillary line. The spleen was not palpable. There was slight swelling of the left elbow joint, but there was no tenderness, and pain was elicited only on extreme extension.

Course—January 26. The temperature ranged from 102.6 to 103.4 F., the pulse was 150, and the respiration rate, 40. There were swelling and ecchymosis

2 We are indebted to Dr. N. E. Brill for the privilege of reporting this case.

of both anterior and posterior surfaces of the arytenoids, and edema of the anterior surface of the epiglottis and in both pyriform fossa. The appearance was that of purpuric laryngitis (note of examination by Dr Yankauer).

January 27 The temperature ranged from 102.8 to 103.2 F, the pulse was 150, and respiration rate, 34. There were diffuse coarse moist rales, which disappeared after the cough. The left elbow joint was no longer swollen.

January 28 The temperature ranged from 102.2 to 104 F, the pulse was 130, the respiration rate, 28.

January 29 The temperature ranged from 104 down to 103.4 F, the pulse was 135, the respiration rate, 26. The signs of fluid at the left base were still present. Over the right lower lobe posteriorly, the breath sounds were suppressed, and there were profuse, inconstant crepitant rales. The lesions on the tongue and lower lip were healing. Several bright red petechiae appeared in the conjunctival mucous membrane of the left lower lid. The fundi showed bilateral neuroretinitis.

January 30 The temperature was 102.4, pulse, 120, respiration rate, 28. Several petechiae appeared in the right lower conjunctiva, one showing a white center.

January 31 The temperature ranged from 102.2 to 104.2 F, the pulse was 130, the respiration rate, 25. The erythematous lesions on the face were more distinct and darker. Several fresh petechiae were present in the conjunctiva of the upper and lower lids of the right eye. One of these had a white center. The signs in the chest were practically unchanged.

February 1 The temperature range was from 103.4 to 104.2 F, the pulse was 120, respiration rate, 36. The general condition of the patient had grown worse. Fresh white-centered petechiae were present in the right lower conjunctiva. A pleuro-pericardial friction rub was heard over the fourth left interspace. There were no murmurs at the valve orifices.

February 2 The temperature range was from 104.2 to 107.4 F, the pulse was 168, respiration rate, 28. The patient was stuporous and somewhat cyanotic. Cheyne-Stokes respiration had set in.

February 3 The neck was rigid, but there were no other signs of meningeal irritation. Over the right lower lobe posteriorly, there was dulness and diminished breathing. The stupor deepened into coma, and the patient died. Shortly before death, the temperature rose to 108 F, the pulse to 190, and the respiration rate to 40.

Laboratory Examinations—These are presented in Table 2.

Necropsy (eight and one-half hours after death)—The body was that of a well developed and well nourished woman. In the left lower palpebral conjunctival mucous membrane, there was a fading petechial hemorrhage.

The heart was somewhat enlarged. The pericardial investment of the right auricle was roughened, lusterless and covered by a thin layer of fibrinous exudate. There were friable fibrinous adhesions between the parietal pericardium and the left pleura. Numerous small hemorrhages of irregular outline were found beneath the visceral pericardium, especially over the auricles. The tricuspid orifice admitted four finger tips. The tricuspid valve showed patchy fibrous thickening suggestive of a previous attack of endocarditis. Along the line of closure, there was a discontinuous row of granular grayish pink verrucous vegetations, most extensive in the region of the anterior and median cusps, where the lesions were spread over an area of 0.5 cm in diameter (Fig. 3). There was a fine vegetative deposit on the ventricular aspect of the median cusp, whence there had been extension along the chordae tendineae for a distance of a few millimeters. On the left half of the left posterior cusp of the pulmonary valve, there were several minute slightly raised yellowish gray vegetations, and along the line of attachment of both the right and the left posterior cusps, there was a narrow strip of similar vegetative deposit.

The mitral orifice admitted two fingers. The valve showed diffuse fibrous thickening, most marked in the aortic leaflet. In the region of the junction of the two cusps posteriorly, there was a mass of grayish and grayish pink opaque verrucous vegetations, extending from a point 2 mm above the closure line as far as the free edge (Fig 4). There was another group of similar but flatter vegetations along the closure line and free edge where the cusps were joined anteriorly. The endocarditic process, which had also attacked the ventricular aspect of the posterior cusp and the line of attachment of the latter, had spread downward for a short distance along the mural endocardium of the posterior wall of the ventricle. There were several other small patches of mural endocarditis in the left ventricle (Fig 4). One of these was situated on the papillary endocardium, and several others were in the angle between the tips of the posterior papillary muscle. Similar areas were present in the right ventricle. These patches were irregular in outline and had a diameter varying from 2 to 5 mm. Their surface had an opaque, verrucous appearance, the color

TABLE 2.—*Laboratory Examinations*

Urine								
Date	Appearance	Reaction	Specific Gravity	Albumin	Sugar	Microscopic		
1/26	Cloudy	Acid	1.020	+++	0	Hyaline and granular casts		
1/28	Clear	Acid	1.025	+++	0	Hyaline and granular casts, a few erythrocytes		
2/1	Cloudy	Acid	1.020	+++	0	Hyaline and granular casts		
Blood Chemistry								
Date	Urea N, Mg per Hundred Cc 16.8			Uric Acid, Mg per Hundred Cc 2.4			Creatinin Mg per Hundred Cc 1.0	
1/27	Blood Counts							
Hemo globin, per Cent	Red Blood Cells	Color Index	White Blood Cells	Poly-morpho nuclear Neutro- phils, per Cent	Eosino phils, per Cent	Lym- phocytes, per Cent	Mono cytes, per Cent	Mvelo blasts or Mvelo cytes
1/26 75	5,400,000		6.89	5,400	68	1	28	3
1/27 70	3,430,000		5,600	74	0	24	1	1 (myelo blast)
1/29 74	3,620,000		5,200	69.5	0	27.5	1.5	1.5 (myelo cytes)
								80,000
								70,000

* January 29. The bleeding time was two minutes, coagulation time, seven minutes; capillary resistance test, negative; clot retraction, very slight in twenty-four hours. The Wassermann reaction of the blood was negative. A blood culture was made February 2, the mediums used were bouillon and glucose bouillon flasks, agar and glucose agar plates, and Veillon tubes of glucose agar for anaerobic study. All mediums remained sterile.

being a mottled reddish and yellowish gray. The right auricle was the seat of several patches of mural endocarditis (Fig 3). Interspersed among the endocarditic lesions was a number of small hemorrhages. The aortic valve was slightly thickened. Crushings of the vegetations were sterile. The myocardium was turbid and brownish, and showed tigering. The coronary arteries and aorta showed a slight degree of sclerosis.

Examination of the lungs revealed, in the left plural cavity, a small effusion. The right lung showed areas of bronchopneumonia in the middle and lower lobes. Both lungs were voluminous and showed edema and congestion.

The liver was enlarged, weighing 2,000 gm. The parenchyma was fatty and showed cloudy swelling and marked chronic passive congestion.

The spleen was enlarged, weighing 600 gm. The malpighian bodies were enlarged and stood out prominently as grayish nodules against a background of dark red congested pulp.

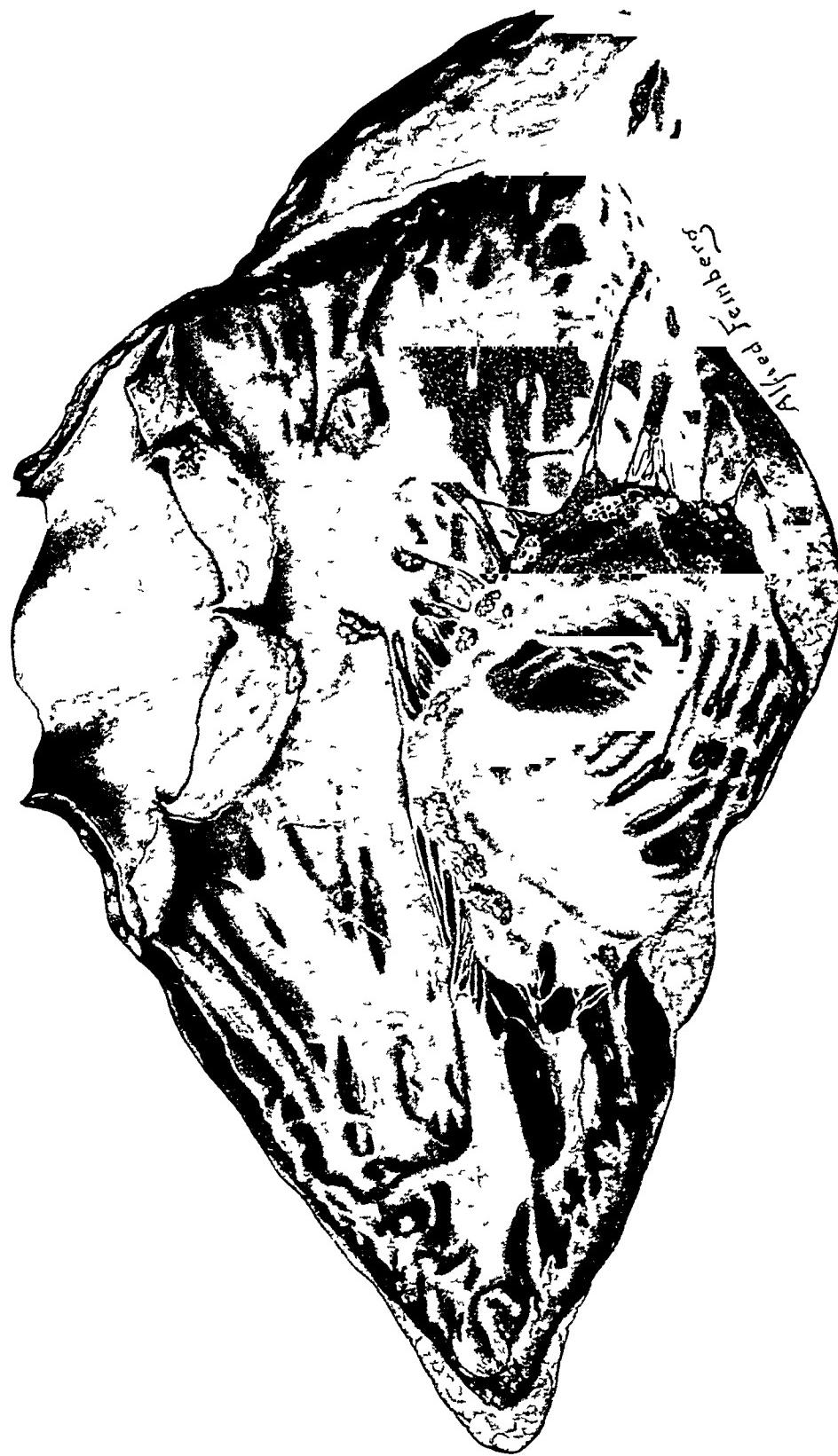


Fig. 3 (Case 2) — Right side of heart. Small flat vegetations are irregularly distributed on tricuspid and pulmonary valves. A narrow strip of endocarditis along the line of attachment of two of the cusps of pulmonary valve may be noted. Patches of mural endocarditis are present in auricle and ventricle

The kidneys were somewhat swollen and less firm than normally. The capsules stripped with slight difficulty, revealing a smooth mottled surface, studded with irregularly distributed minute hemorrhages. The cortical tissue was somewhat swollen and turbid and a grayish pink, but the striations were distinct and the glomeruli are not unduly prominent. The medullary pyramids were congested. Numerous minute hemorrhages were present in the mucosa of the pelvis. The ureters and bladder were normal.

Microscopic Examination.—In the myocardium, the striations of the muscle fibers were indistinct. There was interstitial edema and slight perivascular fibrosis. Here and there were small areas of interstitial round-cell infiltration. There were no Aschoff bodies.

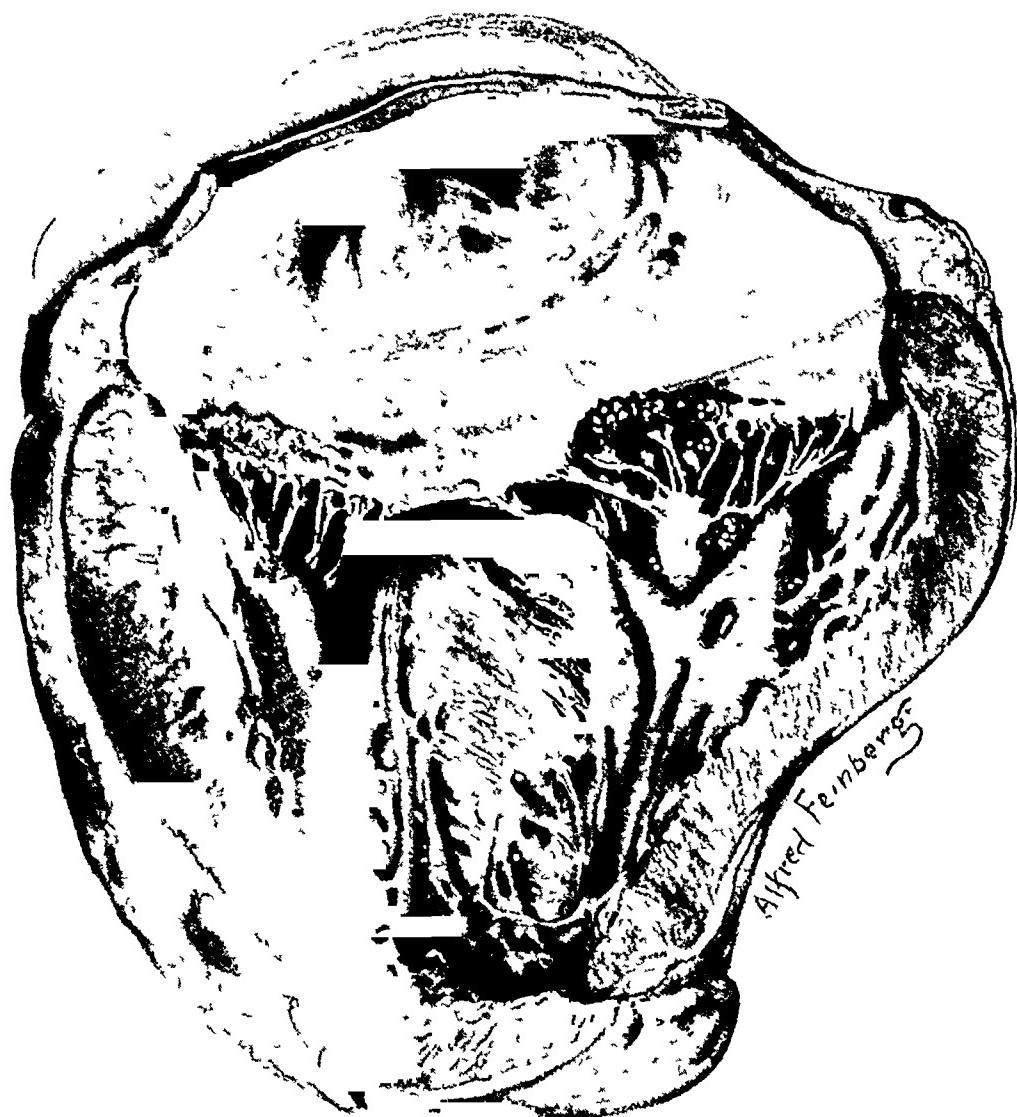


Fig. 4 (Case 2).—Left side of heart. There are verrucous lesions on the mitral valve along the line of closure and the free edge and small islands of mural endocarditis on endocardium of posterior papillary muscle. Extension of the endocarditic process on the mural endocardium of the posterior wall of the ventricle is concealed behind posterior flap of mitral valve.

In the mitral valve were vegetations consisting of a hyalinized thrombus deposited over a fairly extensive area of endocardium. There was but slight cellular infiltration in the subendothelial structures. The vegetations were only in part covered by endothelium. Bacterial stains showed no micro-organisms.

The lungs showed purulent bronchitis and areas of bronchopneumonia. The unaffected alveoli were the seat of marked hemorrhagic extravasation.

The liver showed chronic passive congestion and parenchymatous degeneration. There was marked fatty infiltration of the liver cells in the inner zone of the lobules.

Examination of the spleen showed that the capsule was thickened and there was an organized fibrinous deposit on its surface. The malpighian bodies were large and showed marked diminution of the lymphoid elements. The greater part of each malpighian body was occupied by a number of arterioles, each of which was surrounded by a broad zone of hyaline-like connective tissue. The arteriolar lumen in each instance was diminished in caliber. There were intense congestion of the pulp and dilatation of the venous sinuses.

The kidneys showed congestion, tubular degeneration and medullary edema. There was no glomerulonephritis. The arteries showed atherosclerotic thickening of moderate degree.

COMMENT

The clinical phenomena presented by this patient differed in certain respects from those observed in the previous case. The patient, who had been suffering from polyarthritis for some months, sought medical aid because of the development of a severe respiratory infection, and, in the hospital, the laryngeal symptoms and the presence of pneumonia distracted attention from the heart. The detection of the endocarditis was particularly difficult because of the absence of murmurs and cardiac enlargement. The only finding indicative of infection of the heart valves was the presence of white-centered petechiae in the conjunctival mucous membrane. The friction rub, which proved to be due to pleuro-pericarditis, might have occurred in the absence of endocarditis. The eruption on the face was of the greatest interest, as a similar eruption was observed in another case of this series. The dermatologists were unwilling to identify these lesions as acute lupus erythematosus disseminatus, but stated that there was a close resemblance. Certain manifestations suggested a tendency to purpura: (1) the hemorrhages into the inflamed laryngeal mucosa, and (2) the low platelet counts and the marked diminution of clot retractibility. Further peculiarities of the underlying infection were the ulcerative lesions of the oral mucosa, the enlarged spleen, the bilateral neuroretinitis and the persistent leukopenia. An attempt to grow organisms from the blood, both aerobically and anaerobically, gave negative results. The postmortem examination, as in the previous case, revealed the lesions of the atypical form of endocarditis.

CASE 3—History—S. H., a youth, aged 19, admitted to the Mount Sinai Hospital Sept. 16, 1913, with a negative family history, did not remember having any of the acute fevers of childhood. One month before the onset of the present illness, he had an infection of the finger, followed by lymphangitis. Improvement followed incision of the forearm. For six months preceding his admission to the hospital, he had recurrent attacks of pain and swelling in various joints, particularly in the interphalangeal elbow and knee joints. The articular symptoms rarely lasted more than a few days at a time. Five months before admis-

sion, he developed effusion into both knee joints. Two months later, he developed transient hematuria, following the administration of vaccines. The joint symptoms persisted to the time of admission.

Physical Examination—The patient was well developed and well nourished. The temperature was 101 F. There was no edema, dyspnea or cyanosis. The pupils were equal and regular, reacted to light and contracted during accommodation. The pharynx was negative. Scattered over the skin of the anterior aspect of the chest and the upper arms was a diffuse erythematous eruption, interspersed with small irregular areas of purpura. Scattered over the lower extremities were large red blotches of subcutaneous hemorrhage. The lungs were clear. The heart was not enlarged, and the apex beat was in the left fifth interspace in the mammillary line. The action was rapid and regular, and there were no murmurs. The pulses were equal and the rhythm was regular. The pulse rate was 100. Neither the liver nor the spleen was palpable. There was slight stiffness of both knee joints, the left shoulder joint and all the finger joints. There was no articular swelling. The reflexes were normal.

Course—September 17 The temperature was 101.2 F., the pulse, 88, the respiration, 22. The systolic blood pressure was 135. September 20 The coagulation time of the blood was four minutes. September 23 The temperature was 98.6 F. The erythematous eruption had disappeared and the purpuric spots were fading. In the last few days, a few small erythematous tender nodules appeared over the elbows and finger tips. Each of these disappeared within twenty-four hours. September 25 The Pirquet test was negative. September 30 The temperature was 100.8 F., pulse, 100, respiration, 24. The cutaneous rash had completely disappeared. The patient developed a painful, tender node over the left wrist yesterday. October 2 A rough systolic murmur was audible over the pulmonic area. October 14 The temperature was 100.2 F., pulse, 98, respiration, 24. The interphalangeal joints of both hands were swollen and almost immobile, but there was no pain or tenderness. October 26 November 3 The temperature was 103.8 F., pulse, 138, respiration, 24. For the last two weeks, the temperature had ranged between 98 and 101.8 F.

November 10 Roentgenographic examination of the chest revealed bilateral pleural effusion and great enlargement of the cardiac shadow. November 13 For the last three days, the patient had had a feeling of weight over the precordium. The murmur over the pulmonary area was now scarcely audible.

November 14 The temperature was 103 F., pulse, 128, respiration, 32. A dry leathery pericardial friction rub appeared over the precordium. The patient now complained of definite precordial pain. The apex beat was felt 9.5 cm to the left of the midsternal line in the fifth interspace. The left border of the heart was found by percussion to be 10 cm lateral to the sternum in the fifth interspace, and the right border 3.5 cm to the right in the fourth interspace. November 15 The temperature was 103.4 F., pulse, 148, respiration, 46. The precordial pain disappeared, but the patient's general condition was worse lateral to the sternum.

November 17 The temperature was 103.2 F., pulse, 142, respiration, 32. The patient complained of sore throat. The left border of the heart, as determined by percussion, was now 13 cm to the left of the midsternal line in the fifth interspace and the right border, 7 cm to the right in the fourth interspace. The physical signs pointed to pericardial effusion. There was flatness at the left base, below the level of the angle of the scapula. Over the right base, there was flatness and diminished breathing, beginning 3 cm below the level of the angle of the scapula.

November 24 The temperature was 100.2 F. The friction rub had disappeared. There was a short rough systolic murmur over the pulmonary area. No murmurs were heard over any of the other valve orifices.

November 28 The temperature was 102 F., pulse, 134, respiration, 24. The friction rub was again audible.

December 1 The temperature was 102 F. The signs pointing to bilateral effusion were more marked.

December 3 Five cubic centimeters of sterile, bloody fluid were obtained by aspiration of the left pleural cavity. The cell count was polymorphonuclears, 15, mononuclears, 85. Roentgenologic examination (Dr. Jaches) revealed no abnormalities in the bones of the hands.

December 9 The temperature was 102 F., pulse, 148, respirations, 28. The patient vomited several times. The stool showed occult blood. Petechiae were present over the anterior aspect of the chest and abdomen.

December 10 The patient had a generalized convulsion in the morning lasting two minutes, and shortly thereafter died.

Temperature Curve—September 16-22 The temperature was irregularly remittent, varying from 99 up to 101.4 F., and once reaching 102.6 F.

September 23-October 13 The temperature was usually 98.6 to 99.6, occasionally, 100.6 F.

October 14-25 There were occasional rises to 101.2 F.

October 26 The range was from 103 to 103.8 F.

October 27 The range was from 101.4 to 102.6 F.

October 28-November 3 The temperature ranged from 98 to 101 F.

November 4-10 The temperature was 98.6 to 101.8 F.

November 11-17 There was a gradual irregular rise, in the first few days up to 101.8 F., later to 103.4 F.

November 18-24 The range was from 98.4 to 101.4 F.

November 25-December 4 The temperature was usually 100 to 102 F., at times reaching 103.4 F.

December 5-8 The temperature was not over 100 F.

December 9 The range was from 100 to 102 F.

Laboratory Examinations—These findings are presented in Table 3.

TABLE 3—*Laboratory Examinations*

Urines †							
Date	Appearance	Reaction	Specific Gravity	Albumin	Sugar	Microscopic	
9/17 10/30	Clear	Acid	1.030	0	0	Negative	
	Clear	Acid	1.024	0	0	Few hyaline casts	numerous leuko-
11/22	Clear	Acid	1.020	+	0	cytes and epithelial cells	
12/ 9	Clear	Acid		+	0	A few leukocytes, occasional hyaline	
						casts	
						Hyaline casts	leukocytes

Blood Counts								
Date	Hemo-globin, per Cent	Red Blood Cells	Color Index	White Blood Cells, 8,600	Poly-morpho-nuclear Neutrophils, per Cent	Eosino-phils, per Cent	Small Lymphocytes per Cent	Large Lymphocytes, per Cent
9/17	70	5,000,000	0.7	8,600	55	1	32	11
9/22								
10/27								
11/15	60	3,680,000	0.82	10,300	74	0	24	2
				10,200	76	0	16	8

* The Wassermann reaction of the blood was negative. Blood cultures were made October 13 and November 24 both were negative. The mediums used were bouillon and glucose bouillon flasks, and agar and glucose agar plates.

† Amounts varied between 1,100 and 2,300 cc, usually being less than 1,800 cc.

Necropsy (Nine hours after death, Dr. Baehr)—The body was that of a well developed, moderately well nourished young man. On the anterior aspect of the chest and abdomen were a few petechiae.

The heart was somewhat enlarged. The lungs were attached to the parietal layer of the pericardium by friable adhesions. Both layers of the pericardium were markedly thickened throughout, and were covered by a thick, shaggy deposit of organizing fibrinous exudate. The parietal layer of the pericardium had been converted into a tough, leathery membrane, measuring from 3 to 4 mm in thickness. There were multiple friable adhesions between the visceral and parietal pericardium, and within the fibrin meshes there was a good deal of fluid. In the region of the basal portion of the anterior surface of the right ventricle, the adhesions were very dense and quite fibrous. Numerous petechial hemorrhages were scattered over all the pericardial surfaces. The right auricle was dilated. Just above the orifice of the coronary sinus was a slightly raised patch of fibrinous vegetative deposit, measuring 1 by 2 cm. Along its lower border were several petechial hemorrhages. The tricuspid valve admitted four fingers. On all three cusps, there were a number of minute patches of rather flat, yellowish white, opaque, granular deposits situated irregularly along the closure line, extending in places above and below the latter, and also involving the free edge. The infundibular cusp was diffusely thickened, apparently as the result of an old process. Scattered among the endocardial lesions was a number of petechial hemorrhages, the size of a pinhead. The left posterior cusp of the pulmonary valve showed a small patch of a rather flat yellowish white opaque granular deposit, irregular in outline, situated along the line of closure. Spreading downward on the mural end from a point along the line of attachment of this cusp, there was a somewhat elevated area of a yellowish gray opaque verrucous deposit, measuring 0.7 by 0.5 cm. Small flat patches of granular material were present along the line of closure of the anterior and right posterior cusps, and there was a narrow strip of vegetative deposit along the line of attachment of the former cusp.

The left auricle was markedly dilated. The mitral orifice admitted three fingers. Both leaflets of the mitral valve showed marked diffuse thickening, and the edges were rounded. The auricular aspect of the aortic cusp was covered by an extensive plateau-like pinkish gray vegetative deposit, which in places had a granular surface, and in places a verrucous one (Fig. 5). The endocardial lesions extended upward for a distance of 1 cm above the line of closure, and downward to the free edge, extending for a few millimeters along some of the chordae tendineae. On the ventricular aspect of the aortic cusp, there was a patch of similar vegetative deposit, irregular in outline, measuring 1.0 by 0.7 cm. On the auricular aspect of the posterior cusp, there were similar endocardial lesions which on the medical half extended upward along the wall of the auricle for a distance of 1 cm. The free edge was least involved in the lateral half of this cusp. The vegetative process had extended from the ventricular aspect of the posterior cusp downward on the mural endocardium toward the tip of the posterior papillary muscle. Scattered among the endocardial lesions were numerous small hemorrhages. The aortic valve was negative, except for a narrow strip of verrucous deposit along the line of attachment of the right posterior cusp. There was a number of subendocardial hemorrhages in both ventricles. Crushings of the vegetations from various parts of the heart showed no bacteria in smears or cultures. The myocardium was yellowish brown and cloudy in appearance, and of a rather friable consistency. The coronary arteries and aorta were negative.

In the lungs, both pleural sacs showed a considerable quantity of fluid. There were friable fibrinous adhesions between the visceral and parietal pleura of both upper lobes. Both lower lobes were partly collapsed, and showed intense congestion.

In the esophagus and gastro-intestinal tract, there were numerous petechiae on the mucosa.

The liver weighed 2,050 gm. There was present chronic passive congestion. The wall of the gallbladder was markedly edematous.

The spleen was somewhat enlarged, weighing 240 gm. Near the lower pole, there was a small infarct 0.3 cm in diameter, just beneath the surface. There was marked hyperplasia of the malpighian bodies and congestion of the pulp.

The two kidneys weighed 250 gm. There were numerous small hemorrhages in the perirenal connective tissue. The capsules stripped easily, and the surface was smooth and reddish brown in color. The stellate veins were con-

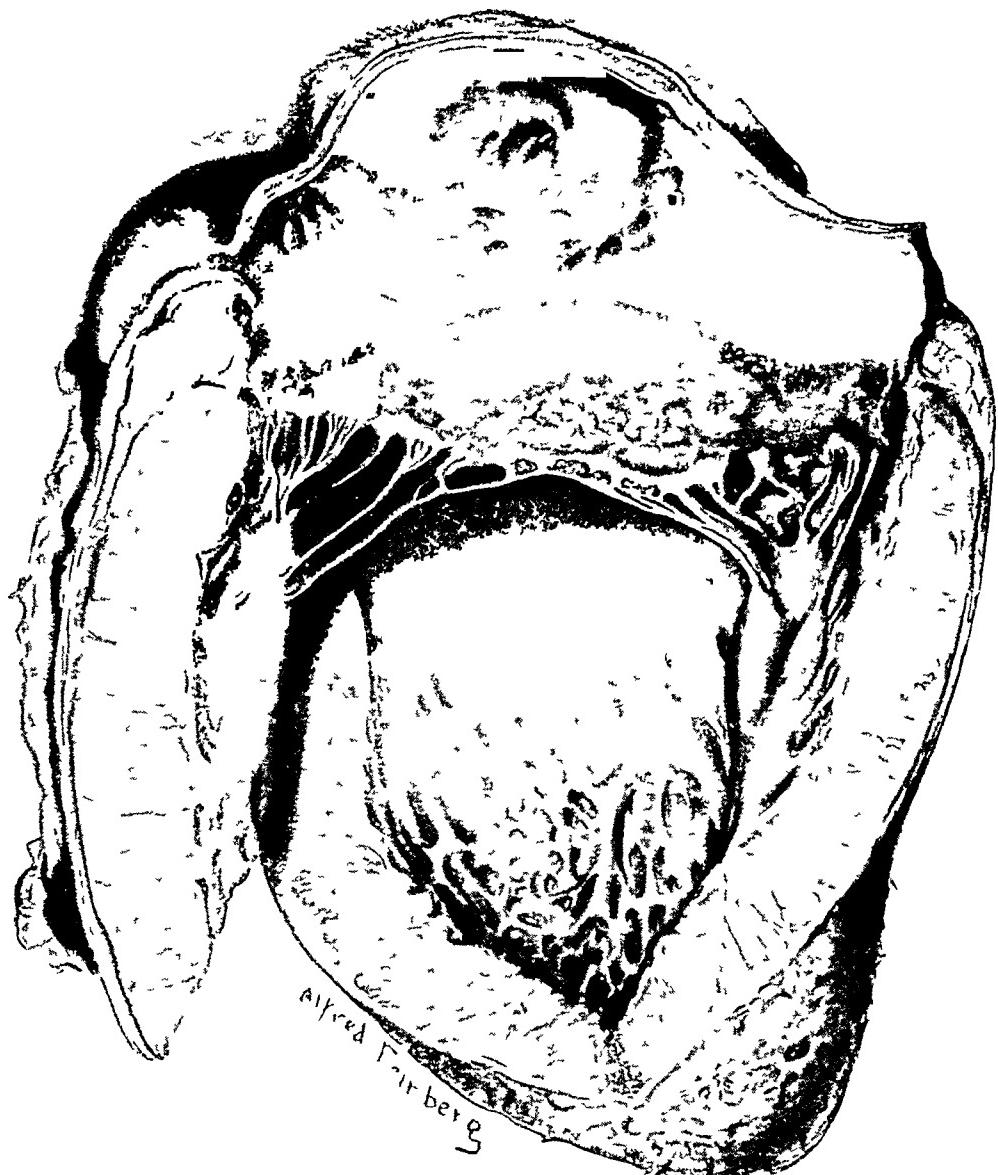


Fig 5 (Case 3) —Left side of heart. There are extensive flat vegetations on mitral valve and small patches of mural endocarditis on the posterior wall of the ventricle behind the chordae tendineae attached to posterior flap of valve. Universal healing fibrinous pericarditis is present.

gested. The glomeruli were large and prominent. There was intense congestion of the medulla. The mucosa of the pelvis and ureters showed numerous petechiae.

Microscopic Examination.—In the mitral valve, there was a deposit of agglutinated blood platelets over large flat areas, beneath which the subendocardial tissues were densely infiltrated with polymorphonuclear leukocytes and round cells, and showed areas of hemorrhage, both recent and old (Fig 6). The valve itself was enormously thickened owing to an old chronic inflammatory process. Here and there, the dense connective tissue was irregularly infiltrated with round and polymorphonuclear cells. The subendothelial structures were very vascular, and here and there a vessel was almost completely occluded by actively proliferating endothelial cells. The blood platelet masses showed a



Fig 6 (Case 3).—Ventricular aspect of mitral valve and chorda tendinea. The valve is greatly thickened. There is an extensive superficial deposition of hyalinized blood platelet thrombotic material, partially covered by endothelium, with old scarring and recent fibroblastic invasion and vascularization in sub-endocardial structures. Focal and diffuse cellular infiltrations, consisting chiefly of polymorphonuclear leukocytes may be noted. There are several small areas of hemorrhage in the deeper layers. On the right is a valvular attachment of greatly thickened chorda tendinea, along which the inflammatory process has spread.

tendency in places to fibroblastic invasion. The inflammatory process extended throughout the entire thickness of the valve, and the vegetative deposit was therefore present on both the auricular and the ventricular aspects of the valve. The vegetative lesions were covered in places by a layer of endothelium.

The chordae tendineae in the neighborhood of their valvular attachments were greatly thickened and showed a deposition of hyalinized thrombus material, and infiltration of the subendothelial structures with polymorphonuclear and round cells. The mural endocardium of the posterior wall of the left ventricle, below the line of attachment of the posterior cusp of the mitral valve, showed extensive deposition of blood platelet thrombotic deposit and infiltration with polymorphonuclear and round cells. The deeper layers showed fibroblastic invasion and fibrous tissue production, and partial destruction and replacement of the underlying muscle fibers. The tips of the posterior papillary muscle and the chordae tendineae near the papillary attachment showed similar changes. No bacteria were present in sections of both the valvular and mitral lesions.

Examination of the pericardium and myocardium showed that the pericardium was greatly thickened. The most superficial layer consisted of masses of fibrin, in the meshes of which were collections of polymorphonuclear cells and a few round cells. Beneath this, there was a layer of loose connective tissue containing numerous fibroblasts and new-formed blood vessels diffusely infiltrated with polymorphonuclear cells. Beneath this layer was a loose connective tissue which was relatively avascular and contained a few cells. Striations of the muscle fibers were somewhat indistinct. There were no Aschoff bodies and no Bracht-Waechter lesions. Special bacterial stains failed to show microorganisms in either the pericardium or the myocardium.

In the liver, there was marked chronic passive congestion, with atrophy of the liver cells in the center of the lobules, and fatty infiltration of the cells in the outer zone. The connective tissue was densely infiltrated in places with round cells.

In the kidneys, the glomeruli showed nuclear increase and a bloodless condition of the capillary loops, resulting from endothelial swelling and proliferation. Many of the glomeruli contained albumin in the capsular space. All the glomeruli were affected, the picture being that of a very early stage of acute diffuse glomerulonephritis. Scattered through the interstitial tissue of both the cortex and medulla were a number of small areas of round-cell infiltration. The medulla showed marked congestion.

In the spleen, the malpighian bodies were marked by hyperplastic. The pulp showed extreme congestion, with dilatation of venous sinuses.

Comment—The simultaneous occurrence of polyarthritis, endocarditis, pericarditis, and negative blood cultures strongly suggested the diagnosis of rheumatic fever, but certain other findings militated against the latter diagnosis. The record states that the patient developed a number of ephemeral tender erythematous nodes soon after coming under observation. These nodes were apparently identical with the Osler nodes observed in subacute bacterial endocarditis, but they are not seen in rheumatic cases. Moreover, when the patient was first examined, he exhibited a generalized purpuric and erythematous rash of a type we have never observed in a proved case of rheumatic fever. Shortly before death petechiae and acute glomerulonephritis made their appearance. White-centered petechiae do not occur in rheumatic endocarditis, and petechiae without white centers occur in the latter disease only in association with purpura. Unfortunately, no note was made as to whether or not the petechiae observed in this case had white centers. On the other hand, we have not encountered acute glomerulonephritis in a case of rheumatic fever in which the diagnosis could be

established by the finding of Aschoff bodies in the myocardium. The endocardial lesions found at necropsy were clearly not rheumatic and proved to be of the peculiar type that characterizes the cases constituting the basis of the present communication.

CASE 4—History.—B. M., a girl, aged 10½ years, admitted to the pediatric department of Mount Sinai Hospital, July 24, 1911, had an unimportant family history. She had had measles in infancy, but no other febrile diseases. Ten weeks before admission, she developed pain in both wrists, elbows and shoulders. There were also occasional pains in the joints of the lower extremities. Fever had been present from time to time since the onset. During the week preceding admission to the hospital, the articular pains became less intense, but the patient began to complain of precordial pain, cough, shortness of breath and palpitation. The bowels became constipated and the urine scanty.

Physical Examination.—The patient was well nourished and well developed. The temperature was 101.4 F., pulse, 136. Her respiration was somewhat accelerated but not labored. On the skin of the bridge of the nose, extending laterally over both cheeks, there was an erythematous eruption of butterfly pattern, which resembled acute lupus erythematosus disseminatus. The skin of the upper part of the anterior aspect of the chest showed patches of erythema. There was brownish pigmentation of the skin over the abdomen. The posterior cervical and axillary lymph nodes on the left side, and the inguinal nodes on both sides were somewhat enlarged. The pharynx was normal. There was slight dulness and suppression of the breath sounds in both lower axillary regions. Posteriorly, there was flatness, extending from a point just above the angle of the scapula to the extreme base on both sides. Here, the breath sounds and the spoken sounds were distant, and there was absence of the whispered voice sounds.

The heart was slightly enlarged, the right border extending 2.5 cm lateral to the midsternal line in the fourth interspace, the left border being 1 cm lateral to the mammillary line in the fifth interspace, and the right border 2.5 cm to the right of the midsternal line in the fourth interspace. The cardiac impulse was seen and felt in the second and third interspace, 2.5 cm lateral to the mammillary line. The heart action was rapid but regular. A loud, blowing, systolic murmur was audible over the entire precordium. Just within the apex, there was a loud presystolic rumble followed by a snapping first sound. The second pulmonic sound was loudly accentuated. The pulse rate was 136 and the rhythm regular. The abdomen was somewhat distended and tympanitic. The liver was enlarged, extending 7.5 cm below the costal margin in the mammillary line. The spleen was not felt. There were tenderness and slight limitation of motion of the right wrist joint, the proximal interphalangeal joint of the fifth finger of the left hand, the interphalangeal joints of the right hand and the right knee joint.

Course.—July 26. The temperature was 100.4 F., pulse, from 136 to 152, respiration rate, 60. Exploratory puncture of both pleural cavities gave negative results. The Pirquet test was positive.

July 30. The temperature was 101 F., pulse, 130, respiration, 32. A rough pericardial friction rub was audible over the left fourth interspace close to the sternal border.

July 31. The temperature was 104 F., pulse, 152, respirations, 48.

August 10. The temperature dropped to 100 F., but the pulse was still rapid (130). The pericardial friction rub was ephemeral. There was no precordial pain, dyspnea or cyanosis.

August 16. The temperature was 101.4 F., pulse, 124. There were slight dyspnea and palpitation, and mild cyanosis of the finger tips. The left border of the heart, as determined by percussion, was 3.5 cm lateral to the mammillary

line. The friction rub was not heard. A soft, mitral, systolic murmur was heard in the region of the apex. The interphalangeal joints were swollen, but were neither painful nor tender.

August 19 The temperature was 101 F., pulse, 168, respiration, 68. The joint manifestations had become more marked. There was a peculiar blueness of the fingers, most marked over the swollen proximal interphalangeal joints. The joints of the toes were also swollen, and there was blueness of the skin over both ankles and knees. There was no tenderness, pain or impairment of function of any of the affected joints. A few moist râles were audible over the left upper lobe anteriorly. In the interscapular space, there was an area of dulness, bronchovesicular breath sounds and moist râles. Over the right base anteriorly, there were numerous subcrepitant râles. The pericardial friction rub was again audible. The liver and spleen could not be felt.

August 22 The temperature was 100.4 F., pulse, 152, respiration, 40. Petechiae appeared for the first time. Several were present in the conjunctival mucous membrane of the right lower lid and in the right bulbar conjunctiva.

August 24 The temperature was 99.8 F., pulse, 122, respiration, 36. The conjunctival petechiae were fading. A number of petechiae appeared on the back of the shoulders and a few on the abdomen. The cardiac impulse was diffuse and was seen and felt in the second, third and fourth interspaces. The left border of the heart was 9 cm lateral to the midsternal line in the fourth interspace. The first sound at the apex was followed by a soft systolic murmur. The friction rub was not audible. There was flatness in the left lower axilla and over both lower lobes posteriorly, beginning at the angle of the scapula. Here the tactile fremitus and breath sounds were diminished and a few subcrepitant rales were heard.

August 25 Petechiae had become more profuse over the neck, back and shoulders.

September 7 The temperature was 99 F., pulse, 112, respiration, 36.

September 11 The temperature was 99.6 F. at 4 p.m. Several hours later, the patient had a sudden attack of dyspnea and cyanosis, with twitchings of the face, left arm and left leg. For a short period, she was unconscious.

September 12 The patient was somewhat stuporous and the temperature rose to 103.4 F. The left leg was paralyzed. The knee jerk was increased on the right side and absent on the left. There was ankle clonus on the right side. The patient vomited several times.

September 13 The temperature was 101.4 F.

September 14 The temperature was 99 F., pulse, 120, respiration, 32. In the morning, the patient had clonic spasms of the left side, lasting five minutes.

September 15 The temperature rose to 102.6 F., and the pulse rate to 164. The patient vomited several times, and died.

Temperature Curve—July 24-30 The curve was irregular from 98 to 102 F.

July 31 The range was from 100 to 104 F.

August 1-13 At first, the temperature was from 98 to 99.6 F., later, 98.6 to 101.6 F.

August 14-20 The temperature ranged from 99 to 102.6 F.

August 21-27 The range was from 98 to 101.6 F.

August 28-September 11 The curve was irregular, from 98.4 to 101 F., and once to 102 F.

September 12 The range was from 101.6 to 103.6 F.

September 13 There was a drop to 98 F.

September 14 The temperature ranged from 99 to 102.6 F.

Laboratory Examinations—These findings are presented in Table 4.

Necropsy (Nineteen hours after death)—The body was that of an emaciated female child. There were a few petechiae scattered over the anterior aspect of the chest on the right side.

The heart was somewhat enlarged. The pericardial membranes were greatly thickened and there were fairly dense adhesions between the visceral and parietal layers. The adhesions were edematous, hemorrhagic and friable, and represented fibrinous exudate undergoing organization. The right auricle was dilated. The tricuspid orifice admitted three finger tips. The valve showed slight diffuse thickening, but no definite evidence of a previous attack of endocarditis. Along the line of closure of the anterior cusp and attached to the free edge there were a few scattered minute granular grayish verrucae in a state of healing. To the right of the tip of the large papillary muscle was a small patch of mural endocarditis, 2 mm in diameter. The pulmonary valve was negative. The left auricle was moderately dilated. The mitral valve showed diffuse thickening and whitening. Attached to the free edge and ventricular aspect of the posterior cusp there was an irregular heaped mass of rather firm granular opaque yellowish white vegetative deposit (Fig 7). The latter was most massive along the ventricular aspect of the posterior cusp, where it reached a thickness of 5 mm. The vegetative process extended to the line of attachment of both cusps whence it spread downward along the mural endocardium of the ventricle surrounding the upper half of the insertion of

TABLE 4.—*Laboratory Examinations**

Urine							
Date	Appearance	Reaction	Specific Gravity	Albumin	Sugar	Nitrate	Microscopic
7/25	Clear, amber	Acid	1.020	Faint trace	0	Negative	
8/7	Clear, amber	Acid	1.025	Heavy trace	0	Negative	
8/26	Clear amber	Neutral	1.012	Heavy trace	0	Red blood cells and finely granular casts	
8/28	Smoky	Acid	1.022	Heavy trace	0	Many red blood cells, leukocytes and coarsely granular casts	
9/4	Smoky	Alkiline	1.018	Heavy trace	0	Numerous red blood cells and white blood cells, and coarsely granular casts	

Blood Counts						
Date	White Blood Cells	Polymorphonuclear per Cent	Eosinophils, per Cent	Small Lymphocytes, per Cent	Large Lymphocytes, per Cent	Monocytes, per Cent
7/26	6,400	66	4	30	0	0
8/1	6,000	71	2	22	4	1
8/15	6,600	72	4	32	0	0
8/19	8,400	78	0	16	6	0
8/31	10,000	84	0	14	2	0

* Blood cultures were taken July 31, August 29 and September 14. There was no growth.

both papillary muscles in crescentic fashion. The papillary endocardium was intact. As the vegetations passed behind the chordae attached to the posterior papillary muscles, they extended forward and downward along the endocardium of the interventricular septum in the form of a lingual process (Fig 7). The vegetations also extend upward for a short distance along the ventricular aspect of the aortic cusp of the mitral valve. The aortic valve was negative. The vegetation contained no bacteria in smears, crushings and cultures. The left ventricle was hypertrophied, and the myocardium was brownish and cloudy. The coronary artery and aorta were normal.

The lungs showed congestion and areas of bronchopneumonia.

The tracheobronchial and mediastinal lymph nodes were enlarged and firm, and showed gaseous tuberculosis.

The liver was enlarged weighing 1,500 gm, and showed the typical nutmeg appearance of advanced chronic passive congestion.

The spleen (weight 150 gm) was enlarged for the size of the child. The capsule was thickened and adherent at numerous points to the diaphragm and

abdominal wall. Beneath the surface were two small wedge-shaped infarcts, the larger the size of a pea. The malpighian bodies were hypoplastic and the pulp showed congestion.

The two kidneys weighed 300 gm. The capsules stripped readily, revealing a smooth surface, grayish brown and studded with numerous small hemorrhages of variable size. There were present marked cloudy swelling and intense congestion. Some of the glomeruli could be made out as tiny red points.

Microscopic Examination.—Myocardium and pericardium showed that the striations of the heart muscle were somewhat indistinct. There were scattered areas of perivascular scarring and round-cell infiltration. Neither Aschoff bodies nor Bracht-Waechter lesions were present. The pericardium



Fig. 7 (Case 4).—Left side of heart. There are vegetations along the line of closure of the aortic cusp of the mitral valve and along the free edge and ventricular aspect of posterior cusp. Extension of the endocarditic process from the line of attachment of the valve downward along the wall of the ventricle and the tips of both papillary muscles, and further spread of the vegetative process on both sides of papillary muscles may be noted. There is a tongue-like projection of vegetative mass on endocardium of interventricular septum.

was markedly thickened, consisting of a layer of edematous tissue infiltrated with round cells and containing numerous dilated blood vessels. Beneath this, there was a layer of vascularized fibrous tissue.

In the mitral valve, the vegetations consisted of a thick layer of thrombotic material attached to the valve by a broad base. The thrombus deposit consisted of pink-staining, partly hyalinized material, representing altered blood platelet

masses, and blue-staining material. Special stains showed no bacteria. In the deeper layer, there was a great deal of vascularized connective tissue containing large numbers of fibroblasts, oval mononuclear cells, round cells and a few polymorphonuclear leukocytes. Phagocytic cells containing yellowish brown pigment were also present.

The lungs showed an advanced grade of chronic passive congestion, with necrosis of the cells in the center of the lobules and marked dilatation of the sinusoids, and fatty infiltration of the cells in the periphery.

Examination of the spleen showed that the malpighian bodies were hyperplastic. Many of the arterioles of the latter showed swelling and proliferation of the endothelium and a variable degree of narrowing of the lumen. Several of the arterioles were plugged with blue-staining thrombotic material, representing small emboli. The pulp showed marked congestion and moderate hyperplasia. The cells lining the venous sinuses were swollen and prominent. Just beneath the capsule was a small healed infarct.

The tracheobronchial lymph node showed an area of caseation, surrounded by a rim of lymphoid tissue containing numerous Langhans' giant cells.

Comment.—The tentative diagnosis at the time of observation was subacute bacterial endocarditis. The main findings were the subacute febrile course, organic mitral lesions, arthritic symptoms, pericarditis, crops of petechiae, eruption on the face resembling acute lupus erythematosus disseminatus, pneumonia and negative blood cultures. The fever, valvular lesion and petechiae strongly suggested the presence of subacute bacterial endocarditis, but doubt would be thrown on the diagnosis if the patient were observed at present, because of the pericarditis, peculiar cutaneous eruption and negative blood cultures. As will be discussed in detail later, a universal fibrinous pericarditis does not occur in subacute bacterial endocarditis as a part of the disease, and, similarly, cutaneous lesions of the character observed in this patient occur in the latter rarely if at all. The failure to grow organisms from the blood does not exclude the presence of subacute bacterial endocarditis.

The bluish discoloration of the painless, swollen joints deserves mention. This finding does not occur in any of the well-recognized forms of endocarditis. The unilateral twitchings and paralysis, and the disturbances of consciousness which occurred several days before death, may have been due to small cerebral emboli, although this cannot be stated with certainty because permission was not granted for an examination of the brain. Embolism does occur in the atypical form of endocarditis as is manifested by the presence of small splenic infarcts in three of the cases.

At the postmortem examination, it was recognized that the endocarditis was of a peculiar type, particularly because of the unusual manner of spread of the endocardial lesions along the posterior wall of the left ventricle. The vegetations were carefully studied for the presence of bacteria, but none were found, yet the histologic examination of the endocardial lesions revealed an active inflammatory process.

It is true that in rheumatic endocarditis one finds active inflammation in vegetations from which bacteria cannot be isolated, but the localization and the gross and microscopic appearance of the endocardial lesions in the case described above were entirely unlike the findings in rheumatic endocarditis. On the other hand, if the lesions were those of active subacute bacterial endocarditis, large numbers of bacteria would have been found in the vegetations.

GENERAL COMMENT

1. Morbid Anatomy.—A summary of the pathologic findings observed in our four cases will serve to demonstrate the characteristic lesions of the atypical form of endocarditis and will furnish a basis of comparison for cases observed in the future. In three of the four cases, there was a universal organizing fibrinous pericarditis with friable adhesions between the visceral and parietal layers. In one of these, there was also a sterile pericardial effusion. The pericarditis in the three cases could not be regarded as a terminal infection, as the pericardium showed great thickening, with evidences of advanced organization of the pericarditic exudate. The microscopic examination in one instance revealed marked leukocytic infiltration of a different character from that seen in rheumatic cases. In no instance were micro-organisms found in sections especially stained for their demonstration. In Case 2, there was no exudate on the visceral pericardium, but there was a localized fibrinous deposit on the parietal pericardium, resulting in adhesions to the adjacent pleura.

The distribution of the endocardial lesions is shown in Table 5.

TABLE 5.—*Distribution of Endocardial Lesions*

Tricuspid valve	4
Pulmonary valve	2
Mitral valve	4
Aortic valve	2
Right auricle	2
Left auricle	1
Right ventricle	1
Left ventricle	4

The vegetations on the mitral valve were situated for the most part on the closure line and generally extended both above and below the latter, involving the free edge in places. The lesions in two instances had a definitely verrucous character, in the one being grayish pink and opaque, and in the other more grayish, fibrous and more translucent. The individual verrucae varied in size from 1 to 4 mm., and had in places a rather broad attachment to the valve. In one case, the vegetation had a very extensive attachment to the mitral valve and, though slightly elevated, the lesions had a rather flat surface. In Case 4, the lesions

on the posterior cusp of the mitral valve were situated chiefly on the ventricular aspect of the valve. The mode of extension of the vegetative process from the mitral valve to the mural endocardium was rather characteristic. In each instance, the inflammatory process had spread from the ventricular aspect to the posterior cusp of the mitral valve and the line of attachment of the latter downward along the mural endocardium of the posterior wall of the ventricle for a variable distance. Two of the cases showed small isolated patches of mural endocarditis in the left ventricle, and two in the right ventricle. In one of the former, there was a fairly large area in the region of the apex of the left ventricle (Fig. 1).

All four cases showed lesions on the tricuspid valve, in each instance affecting only a part of the circumference. Here, the lesions were smaller than on the mitral valve, were more irregularly distributed, and were but slightly elevated above the surface. Of special interest was the involvement of the pulmonary valve, as the latter valve is rarely, if ever, involved in rheumatic fever and is very uncommonly affected in subacute bacterial endocarditis.

In Cases 2 and 3, there were small irregular flat lesions on the ventricular aspect of the valve and along the line of attachment of the latter to the ventricle. Two of the cases showed small lesions on the aortic valve. In one of these, there was a narrow strip of endocarditis along the line of attachment of one of the cusps. In two instances, there were flat lesions of irregular outline on the endocardium of the right auricle. Interspersed among the vegetations on the valvular and mural endocardium, there were numerous small hemorrhages. The myocardium showed a variable degree of parenchymatous degeneration, and in one case showed definite fatty changes. The coronary arteries and aorta showed a slight degree of sclerosis.

The microscopic findings were not uniform, but presented certain characteristics in common. The vegetative lesions on the heart valves were capped by blood platelet thrombus deposit showing various degrees of hyaline change. In places, the vegetations were covered with endothelium but large areas remained denuded. In the deeper layers, there were focal and diffuse cellular infiltrations, chiefly of round cells in three of the cases, and predominantly of polymorphonuclear cells in the remaining one. Scattered among the inflammatory foci were numerous small hemorrhages. In places, the entire thickness of the valve was affected by the inflammatory process. The valves in several instances showed diffuse fibrous thickening of the type resulting from previous attacks of endocarditis. In the older lesions, there were areas of fibroblastic invasion, hyalinization of the newly-formed connective tissue and extensive vascularization. In one case, many of the blood vessels in the mitral valve showed marked endothelial proliferation of the

intima. The mural lesions presented a picture similar to that seen on the heart valves. Here, however, the superficial platelet thrombus deposit was more extensive and more massive, and larger areas were denuded of endothelium. The process extended into subjacent structures, destroying and replacing some of the underlying muscle fibers. There were cellular accumulations in the subendothelial tissues and extensive fibrosis in the deeper layers, indicating healing. In the older lesions, both mural and valvular, there was extensive fibroblastic invasion and fibrosis, and a lesser degree of cellular infiltration. The endocarditic lesions in all cases were free of demonstrable bacteria, as determined by studies of smears, cultures and stained sections. The heart muscle showed no Aschoff bodies and Bracht-Waechter lesions. In one case, there was a slight diffuse interstitial fibrosis in the myocardium.

Two of the cases showed bronchopneumonia, and the other two, fibrinous pleurisy with effusion. The liver in three of the cases was enlarged, and showed chronic passive congestion and a variable degree of parenchymatous degeneration. In the remaining case, the liver was small. The spleen in three was enlarged, weighing 240, 150 and 600 gm, respectively. In two of these, the malpighian bodies were enlarged, and in one, the enlargement was due not to hyperplasia of the lymphoid elements, but to a peculiar hyaline thickening around the arterioles. In one of the two cases in which the malpighian bodies were not enlarged, many of the arterioles in the latter showed marked endothelial proliferation of the intima, with marked narrowing of the lumen. In the remaining case, the spleen was small, weighing only 80 gm. Small splenic infarcts were found in three of the cases.

In each instance, the kidneys showed small hemorrhages beneath the capsule, and the parenchyma showed tubular degeneration of variable degree. Diffuse glomerulonephritis was present in two of the cases, acute in one and subacute in the other. In no instance were the embolic glomerular lesions of subacute bacterial endocarditis found.

2 Clinical Findings—Three of the patients were female and one male, the ages being 10½, 19, 24 and 37 years, respectively. None of the patients complained of symptoms referable to the heart prior to the onset of the fatal illness, and none gave a history of chorea. In three of the cases, the disease was ushered in by arthritic symptoms. The initial complaint of the fourth patient was precordial pain, which was followed by arthritis and the manifestations of acute nephritis. The disease in each instance ran a subacute course, lasting from four and a half to nine months. All had pyrexia of irregular type throughout the greater part of the period of observation. One of the patients (Case 1), whose temperature had risen daily to from 101 to 104 F, showed practically no fever during the last month of her life. Another patient

(Case 2), whose temperature during the period of observation was constantly elevated, fluctuating between 102 and 104.6 F., developed hyperpyrexia shortly before death, the temperature rising to 108 F. In another case (Case 3), the temperature reached from 101 to 102 F. daily, the highest temperature recorded being 103.8 F. In the fourth case (Case 4), the temperature generally rose from 100 to 101.4 F., reaching 104 F. on one occasion. Excessive sweating was not a marked feature and rigors were uncommon. Anemia was noted in each instance and was of moderate severity in all but one case, in which, during the course of six weeks, the hemoglobin percentage fell from 84 to 34, and the erythrocyte count from 5,400,000 to 2,088,000.

The heart showed no great enlargement in any case. Tachycardia was the rule, but at no time was an arrhythmia noted. Murmurs were heard in three cases. In Case 1, the auscultatory signs pointed to mitral insufficiency, and in Case 4, to mitral stenosis and insufficiency. In Case 3, the patient developed under observation a systolic murmur over the pulmonary area. This finding is interesting, in view of the endocardial lesions which were present on the pulmonary valve. In Case 2, no murmurs were heard at any time during the patient's sojourn at the hospital. Three of the patients complained of precordial pain, and in each case a pericardial friction rub was heard. One of these patients developed, in addition, a pericardial effusion. In each instance, the pericarditic manifestations made their appearance at least several weeks before the patient's death. The friction rub heard in Case 2 proved to be pleuropericardial in origin.

Pulmonary symptoms were present in each case. Three of the patients had pleurisy with effusion, and one of these showed in addition outspoken signs of pneumonia. In a fourth patient (Case 4), there were signs of fluid at both bases. She was tapped during life, but no fluid was obtained, and at necropsy no fluid was found, but the method of examination was inadequate to exclude its presence with certainty. Microscopic examination of the lungs revealed areas of bronchopneumonia.

All the patients showed arthritic symptoms, which developed early and recurred from time to time during the course of the illness. The interphalangeal joints, as well as the larger articulations, were affected. The joints were not swollen and red as in typical rheumatic arthritis, and, in two instances, presented certain unusual features. In one case, there were pain and tenderness of the metacarpophalangeal joints of one hand, but, although there was but slight swelling, the overlying skin was of a peculiar red, unlike that seen in typical rheumatic arthritis. In another case, some of the joints were swollen but not tender, and the overlying skin had a bluish color. In the two remaining cases, the joints were painful and tender, and sometimes swollen.

The cutaneous manifestations were of particular interest. All the patients showed petechiae in the skin or conjunctival mucous membrane or both, generally occurring in crops and many having white centers. These petechiae were identical in appearance with those seen in subacute bacterial endocarditis. Two of the patients showed an erythematous eruption of butterfly distribution on the face, which resembled acute lupus erythematosus disseminatus. Both of these patients had erythematous lesions in other parts of the body, and one also showed ulcerative lesions of the buccal and lingual mucosa. A third patient had an eruption involving the entire trunk and extremities, characterized by irregular blotches of purpura interspersed among areas of erythema. In Case 1, a localized bilateral dermatomyositis appeared early in the disease, and later herpes zoster developed.

Because of the friability of the endocardial lesions, embolism can occasionally occur, and, in one instance, the patient experienced symptoms pointing to splenic infarction. Two other cases showed small splenic infarcts at the postmortem examination, but apparently these gave no symptoms during life. One of the patients developed symptoms suggesting cerebral embolism shortly before death, but this could not be confirmed because an examination of the brain could not be made. The finding in one of the cases of tender erythematous nodes which were apparently identical with the Osler nodes seen in subacute bacterial endocarditis is significant because it indicates the possible occurrence of them in the atypical form of endocarditis.

Two of the patients showed acute glomerulonephritis, one at the onset of the disease and the other toward the close. The first of these patients (Case 1) showed albumin, tube casts and erythrocytes in the urine, oliguria, a rise of blood pressure, a marked reduction of the phenolsulphonephthalein output, moderate nitrogen retention, anasarca and convulsions, and finally died in uremic coma. In all probability, the nephritis contributed largely to the severity of the anemia which this patient developed so rapidly. The second patient developed the manifestations of nephritis late in the disease and died in convulsions. The two remaining patients displayed albuminuria and cylindruria, and erythrocytes were present in the urinary sediment, but glomerulonephritis was not found at the postmortem examination.

There seems to be but little tendency to leukocytosis in the instances of the disease thus far observed. In one case, the leukocyte count never rose above 5,600. The highest polymorphonuclear neutrophil percentage noted in this case was 74. In two other cases, the leukocyte counts varied between 6,000 and 10,000, and 8,600 and 10,300, respectively. In Case 1, there was leukopenia early in the disease, later counts rising to 13,400 and 21,600, respectively.

The blood cultures were uniformly negative, despite the employment of methods which gave positive results in more than 90 per cent of the cases of subacute anhemolytic streptococcus and influenza bacillus endocarditis. Special anaerobic methods were not employed.

Certain of the clinical manifestations, it will be observed, bear a striking resemblance to the symptoms included by Osler in the erythema group. Under the latter designation, Osler included a large number of ill-defined and poorly understood cutaneous visceral manifestations, including certain forms of purpura, angioneurotic edema, erythematous rashes, joint symptoms, ulcerative lesions of the skin and mucous membranes, abdominal colic, pericarditis and acute nephritis. Although these diverse symptoms were grouped under a single designation, a unitary etiology was not hypothesized. It is of interest that in Case 26 of Osler's series, there were lesions in the face which resembled acute lupus erythematosus. It is not improbable that a certain relationship exists between the atypical form of endocarditis and certain of the cases included in the erythema group.

3. Differentiation from Subacute Bacterial and Rheumatic Endocarditis.—In certain respects, the atypical cases resemble both subacute bacterial and rheumatic endocarditis, and yet the differences are quite striking. The differences in the cardiac lesions when comparison is made with rheumatic cases, relate especially to the morphology and distribution of the lesions and to the presence or absence of Aschoff bodies in the myocardium. In typical rheumatic endocarditis, the vegetations consist of small grayish and pinkish gray verrucous structures situated in a row along the line of closure of the valve, rarely involving the free edge or the chordae tendineae. The involvement of the mural endocardium is rare, and when it occurs, is practically negligible. The individual verrucae on the heart valves vary in diameter from 1 to 3 mm., those on a given valve being uniform in size as a rule. Not infrequently, the vegetations are attached to the valve by narrow pedicles. The substance of the vegetations is rather firm. They are crushed with difficulty, and are not easily detached from the valve. Microscopically, the vegetative nodules, in the early stages of their development, consist essentially of a mass of agglutinated blood platelets deposited over a localized area of edematous and actively proliferating subendothelial tissue. The denuded endothelium is quickly replaced by new endothelial cells which grow over the platelet nodule from the adjacent uninvolved valvular endocardium.

In cases of the atypical form of endocarditis, the vegetations frequently have a verrucous character, but tend to be larger and less uniform in size than the typical rheumatic lesions and are attached to the valve by a broader base which includes the valve above and below the

closure and frequently also the free edge. Unlike those in the rheumatic cases, the lesions involve the line of attachment of the valves and attack the auricular and ventricular endocardium by extension from the valves, and also in isolated patches. The spread of the vegetative process downward along the mural endocardium of the left ventricle and the widely scattered islands of mural endocarditis are in striking contrast to the picture seen in the rheumatic cases. The involvement of the pulmonary valve in two of the cases may be of special significance, as it is of the rarest occurrence in rheumatic fever. It is significant that none of the four cases showed Aschoff bodies in the myocardium. The failure to find these structures is not conclusive proof of the absence of rheumatic infection, as they are not always present in cases that appear to be definitely rheumatic. On the other hand, had Aschoff bodies been found, we should have been obliged to classify our cases as rheumatic, unless a combined infection could have been demonstrated.

Clinically, the differences relate particularly to the cutaneous manifestations and to the occurrence of embolic phenomena. Erythematous lesions on the face resembling acute lupus erythematosus disseminatus such as appeared in the atypical cases do not occur in rheumatic fever. We have never seen petechiae with white centers in a proved case of rheumatic endocarditis. On the other hand, petechiae both with and without white centers were present in each of the four cases described above.

Embolism, when seen in rheumatic cases, generally has its source from a thrombus in the left auricle, occurring in association with mitral stenosis and not from vegetations on the heart valves. The rheumatic verrucae are too firmly attached to the valve to give rise to embolism, and even should an occasional fragment be dislodged, the resulting embolism would be too small to be significant. On the other hand, all sources of embolism, except the valvular and mural endocarditis, could be excluded in explaining the infarction of the spleen that occurred in three of the four atypical cases. As a rule, the spleen is not enlarged in rheumatic fever, but enlargement is seen when the latter disease is associated with *status lymphaticus*.³ In three of the four atypical cases, the spleen was enlarged, but in no instance was the organ palpable during life.

Positive statements cannot be made at present concerning the significance of the glomerulonephritis and the purpura which occurred in the atypical group. As far as our experience goes, we have never encountered an instance of acute diffuse glomerulonephritis or generalized purpura in a proved case of rheumatic endocarditis. The atypical and rheumatic forms of endocarditis resemble each other in the occurrence

³ It is surprising how frequently rheumatic fever is associated with *status lymphaticus*.

of universal fibrinous pericarditis, in the frequent involvement of the tricuspid valve and in the absence of embolic glomerular lesions of the kidneys.

In subacute bacterial endocarditis, the vegetations are larger, more elevated and more friable than in the atypical cases, and, when situated on the mitral valve, characteristically spread upward along the postero-lateral wall of the auricle and downward on the chordae tendineae. Moreover, involvement of the tricuspid and pulmonary valves is exceedingly uncommon (and usually slight) in subacute bacterial endocarditis in the absence of a congenital lesion. A universal fibrinous pericarditis does not occur except in the presence of some complication, or as a terminal event, with uremia. The essential difference between the endocardial lesions of the subacute and atypical cases is that the vegetations in the former contain large numbers of the characteristic organisms, e.g., the anhemolytic streptococci, influenza bacilli and, rarely, gonococci or other bacteria. Moreover, blood cultures are generally positive in cases of subacute bacterial endocarditis.

In both forms of endocarditis, white-centered petechiae are found in the skin and conjunctival mucous membranes. It is not possible to state definitely at present whether a cutaneous eruption resembling acute erythematous disseminatus can occur in subacute bacterial endocarditis. In a single patient believed to be suffering from the latter disease, a somewhat similar rash was seen. This patient was treated in the open air in a cold atmosphere, and it was not possible to state whether or not exposure to the sunlight and cold played a rôle in the causation of the cutaneous lesions. Unfortunately, a postmortem examination could not be made. Acute diffuse glomerulonephritis with its attendant clinical manifestations occurs in subacute bacterial endocarditis as well as in the atypical cases, but in no instance of the former disease observed thus far have the renal manifestations made their appearance early as in Case 1 of the atypical group.

Emboliism occurs in both types of endocarditis, but in the atypical cases it occurs less frequently, and the resulting infarcts are much smaller than in subacute bacterial endocarditis. We have hitherto regarded the ephemeral tender erythematous nodules (Osler nodes) as pathognomonic of subacute bacterial endocarditis. It is of interest that indistinguishable lesions were recorded as present in one of our cases. On analysis, this finding is not unexpected, as the Osler nodes are due to small arterial emboli. Because of the lesser tendency to embolism in the atypical cases, one should, however, expect to encounter these nodes much less frequently than in subacute bacterial endocarditis.

The so-called Bracht-Waechter lesions, which are so frequently present in the myocardium in cases of subacute bacterial endocarditis, were not found in any of the atypical cases, but as these lesions are not

specific, they have no important differential value. The embolic glomerular lesions described by Loehlein and later studied by Baehr, which are found in almost every case of subacute bacterial endocarditis and have thus far never been found in any other type of endocarditis, were not present in any of our cases.

4 Etiology—We have no clue at present concerning the etiologic agent of the disease. It has already been stated that the blood cultures in each instance were negative, and that there were no demonstrable organisms in the vegetations. Should the anhemolytic streptococcus be isolated from the blood in an occasional case of the disease, it will be necessary to determine whether it is to be regarded as a secondary invader or as indicative of a mixed infection. That the anhemolytic streptococcus is found in the blood in cases of endocarditis in which it is not the causative agent is borne out by the findings of Swift and Kinsella, who were able to grow the organisms from the blood in 83 per cent of a series of cases of rheumatic fever.⁴ As we do not know the causative agent, it cannot be stated with certainty that a unitary etiology obtains for all our cases. It must be left to future studies to determine whether the lesions of the atypical form of endocarditis are due to an undescribed virus or are the extraordinary result of the presence of a known etiologic agent.

5 Diagnosis—In view of the limited number of cases of the disease which have been studied, it is obviously unwise to make dogmatic statements concerning the diagnostic value of any one symptom or group of symptoms. The ensuing remarks are based on the assumption that the clinical findings observed in our cases are the typical manifestation of the disease. The simultaneous occurrence of white-centered petechiae and acute pericarditis seems to be the most valuable diagnostic finding. This combination of symptoms occurs.

(a) In cases of subacute bacterial endocarditis with advanced renal insufficiency, the pericarditis developing as a terminal uremic manifestation. Acute glomerulonephritis develops occasionally during the active stage of subacute anhemolytic streptococcus (and *Bacillus influenzae*) endocarditis. If death results from uremia while the bacteria are still in the blood, the patient may conceivably develop pericarditis shortly before death. We have never observed such a case, but should one be encountered, the blood cultures would probably be positive and the blood would show marked nitrogen retention. In the healed stage of subacute bacterial endocarditis, advanced renal insufficiency is more common, chronic diffuse glomerulonephritis occurring in about 33 per cent of the fatal cases that were completely bacteria-free. We have encoun-

⁴ In contrast to the condition in cases of subacute bacterial endocarditis, no immune reactions to the anhemolytic streptococcus have been found in the cases of rheumatic fever showing bacteremia.

tered one instance of terminal fibrinous pericarditis in a case of this type. The differential diagnosis here presents little difficulty, particularly because white-centered petechiae are not likely to occur in the bacteria-free stage.

(b) In cases of combined subacute bacterial and rheumatic endocarditis. The presence of positive blood cultures would furnish the clue to the correct diagnosis. In each of three cases of combined active subacute bacterial and rheumatic endocarditis observed by us, the anhemolytic streptococcus was grown from the blood. It so happened that none of these patients had a recent pericarditis.

(c) In cases of acute bacterial endocarditis. The presence of a suppurative focus serving as a portal of entry for the pyogenic bacteria, the acute, stormy course, the Janeway lesions and the positive blood cultures will generally permit the diagnosis to be made with ease. In the staphylococcus cases, the petechiae, in contrast to those seen in subacute bacterial and the atypical forms of endocarditis, often have raised white centers. Moreover, pericarditis is not very common in acute bacterial endocarditis, and, when it develops, is prone to become purulent.

(d) In the atypical form of verrucous endocarditis. It will be recalled that three of our four patients displayed white-centered petechiae and acute fibrinous pericarditis, and it appears that the combination of these symptoms in the presence of negative blood cultures will furnish the clue to the diagnosis of many of the cases observed in the future.

The occurrence of an eruption on the face and elsewhere resembling acute lupus erythematosus disseminatus is important if only to attract attention to the possible existence of the atypical form of endocarditis. A similar statement applies to generalized purpura and erythematous rashes of the type included in the erythema group of Osler. We attach great significance to the finding of acute glomerulonephritis in the atypical cases, for we believe that the etiologic agent, or its toxin, has a great affinity for the glomerular endothelium. The occurrence of acute glomerulonephritis has only corroborative value for the diagnosis, however, for it also occurs in subacute bacterial endocarditis. The diagnostic value of this finding would be enhanced if it occurred as an initial symptom, as in Case 1.

In the presence of fever, arthritides, cardiac murmurs, pericarditis, white-centered petechiae, skin rashes of the character described and repeatedly negative blood cultures, the diagnosis should present no difficulties. It seems highly probable, however, that cases will be encountered in which the endocarditic phenomena will be masked by other symptoms. Case 2 is an illustration in point. At no time could murmurs be elicited, in spite of repeated examinations. We have recently observed a patient who appeared to have contracted this disease five

months previously, but as yet no murmurs have appeared. In cases of this kind, a search for white-centered petechiae, unusual cutaneous eruptions, necrotic lesions on the oral mucosa and possibly the skin, embolic phenomena and pericarditis will be required for the detection of endocarditis.

6. Prognosis.—The ultimate outcome of these cases is a matter of conjecture. The immediate cause of death in our cases was uremia in two, pneumonia and, apparently, cerebral embolism in another, and pneumonia in the remaining one. It is highly probable that mild instances of the disease will be observed, and from a study of such cases, it may be possible to determine whether this form of endocarditis is capable of producing chronic valvular defects. As subacute bacterial endocarditis is generally engrafted on diseased valves, it will be important to determine how often the latter infection attacks the valves in cases of atypical verrucous endocarditis. It is quite conceivable that such a superadded infection occurs. There is some evidence, both clinical and pathologic, that recurrences develop in the atypical form of endocarditis. In three of the four cases, there were organic changes in the valves indicative of a previous attack of endocarditis. We have recently had under observation a patient who, we believe, developed the disease. He had fever, white-centered petechiae, acute pericarditis, a valvular defect and negative blood cultures. Several weeks after the acute symptoms had subsided and the temperature dropped to normal, he developed a recurrence of the fever, and a fresh crop of white-centered petechiae appeared. He recovered, and now shows only the manifestations of chronic valvular disease.

SUMMARY

We have had the opportunity of studying the clinical and pathologic findings in four cases of a hitherto undescribed form of endocarditis, which we have for the present described as an atypical form of verrucous endocarditis. In morphology and localization, the endocardial lesions differed from those observed in subacute bacterial, rheumatic and other types of endocarditis. All four valves were involved, and there was a tendency for the inflammatory process to attack the mural endocardium. A uniform finding in our cases was the extension of the endocarditic process from the ventricular aspect of the posterior cusp of the mitral valve along the adjacent mural endocardium of the posterior wall of the ventricle. Isolated areas of mural endocarditis were found in the right auricle and both ventricles. The vegetations were free of demonstrable bacteria and presented a histologic structure which differed in many respects from that of the lesions in other types of endocarditis. The heart muscle showed neither Aschoff bodies nor Bracht-Waechter lesions and the kidneys showed no embolic glomerular lesions.

The disease, in the form in which it attacked young people who had previously had no organic symptoms, ran a subacute course with fever and progressive anemia. Briefly enumerated, the clinical findings were pericarditis, white-centered petechiae, arthritis, erythematous and purpuric rashes, ulcerative lesions of the mucous membranes, pleuropulmonary symptoms, embolic phenomena, enlargement of the liver and spleen, acute glomerulonephritis, a tendency to leukopenia and repeatedly negative blood cultures. Two of the patients had an eruption on the face which resembled acute lupus erythematosus disseminatus. One of the patients is said to have had tender erythematous nodules which were apparently identical with the Osler nodes, previously observed only in subacute bacterial endocarditis.

For reasons stated above, the acute pericarditis, white-centered petechiae and negative blood cultures together appear to have diagnostic value, especially in differentiating these cases from rheumatic and subacute bacterial endocarditis. In certain cases, the chief diagnostic problem appears to be the detection of endocarditis, for the manifestations of the latter may be masked by other symptoms. In such cases, the presence of an eruption on the face resembling acute lupus erythematosus disseminatus or peculiar erythematous and purpuric rashes elsewhere should lead to a search for the other manifestations of the atypical form of endocarditis.

Attention was directed to the similarity of certain of the symptoms to those observed in the erythema group of Osler, and to the existence of a possible relationship between certain instances of the latter and the atypical form of endocarditis. The frequency of the disease and the ultimate outcome of nonfatal cases is a matter of conjecture. Future studies must determine whether this form of endocarditis is a potential cause of chronic valvular disease. The etiology is as yet unknown, and it is suggested that, in future studies, the special methods adapted for a cultivation of filtrable viruses and spirochetes be employed among others in the search for the exciting agent.

THE EFFECT OF AMYL NITRITE, BLEEDING AND EPINEPHRIN ON THE BLOOD PRESSURE AND THE SIZE OF THE CAT'S HEART*

BURGESS GORDON, M.D.

AND

GUY WELLS, M.D.

BOSTON

The experiments described in this paper were undertaken with an idea of comparing the relative changes in heart size and blood pressure which occur during vasoconstriction, vasodilatation and bleeding. It is known that the intravenous injection of epinephrin causes a sharp rise in the arterial blood pressure due largely to vasoconstriction.¹ It is known also that the nitrites cause a rapid fall in blood pressure due to a vasodilatation by direct action on the blood vessels.² Meek and Eyster,³ in carefully controlled roentgen-ray studies on dogs found that there was a reduction in the blood pressure and diastolic size of the heart after a hemorrhage amounting to about 2 per cent of the body weight. Meyer⁴ has shown by roentgen ray that hearts of rabbits decrease in size after bleeding. He reported a case of marked diminution in the heart outline following hemorrhage, with a gradual return to normal after recovery of the patient.

Adult cats were used in these experiments. They were etherized, placed on an animal board, and held firmly in position by means of leg ropes and adjustable side arms at the neck and lower border of the thorax. The board was so constructed that the animals rested on a concave surface of lead supported by a wooden frame work. An opening 4 by 5 inches (10 by 12.5 cm) in diameter in the lead floor directly under the thorax was replaced by a thin aluminum sheet to allow the penetration of the roentgen rays. An 8 by 10 inch (20 by 25 cm) metal tray supported the screen which moved securely in a 12 by 15 inch (30 by 37.5 cm) shelf beneath this lead-aluminum floor, directly under the upper abdomen and thorax of the animal. By a manipulation of the tray in four directions, the film was divided into as many quarters, three

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine of the Harvard Medical School.

1. Cushny, A. R. *The Text Book of Pharmacology and Therapeutics*, Philadelphia, Lea & Febiger, 1918, p. 367.

2. Sollmann, Torald. *A Manual of Pharmacology*, Philadelphia, W. B. Saunders Company, 1917, p. 376.

3. Meek, W. J., and Eyster, J. A. E. *Am. J. Physiol.* **56** 1 (May) 1921.

4. Meyer, E. *Klin. Wchnschr.* **11** (Jan 1) 1922.

of which were at all times cut off from the roentgen rays by means of the lead surfaces, while the fourth rested beneath the aluminum floor. Each quarter was numbered in sequence and designated with the letter of the cat. This method of study permitted a rapid change of films without affecting the position of the animal. A portable roentgen-ray apparatus was used in making the pictures, the tube being held in position 4 feet (12 meters) above the animal by means of an upright standard. The exposure was for ten seconds and the current was of 10 milliamperes backed up by a $4\frac{1}{2}$ inch (11.3 cm.) spark gap.

The procedure for study consisted of taking control pictures until a satisfactory position of the chest was obtained. The femoral arteries

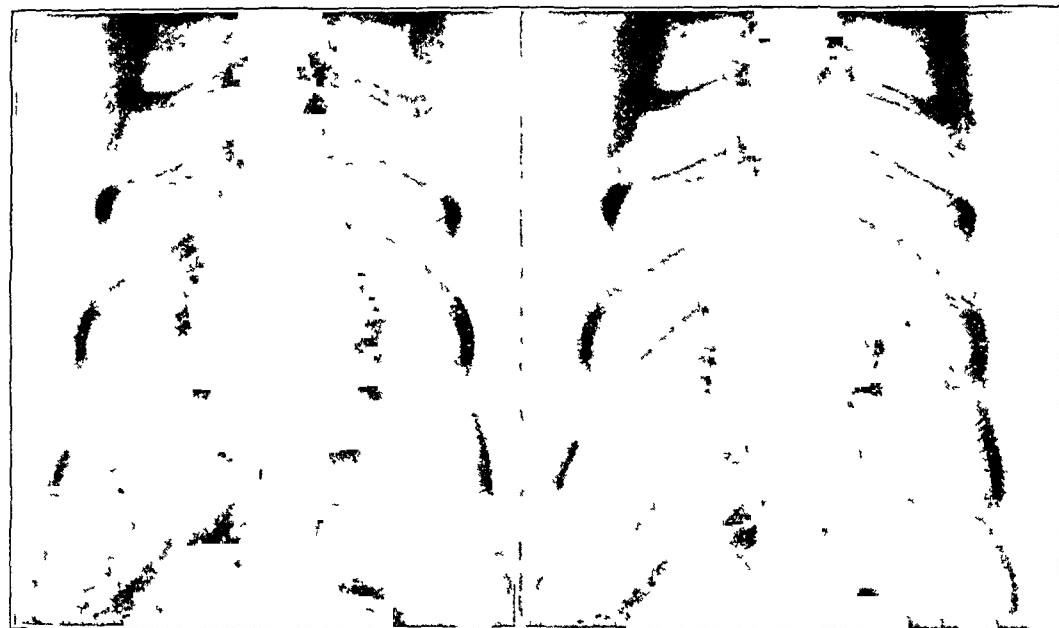


Fig 1.—Corresponding changes in the heart and blood pressure during vasodilatation and vasoconstriction, and after bleeding. The weight of the silhouettes is expressed in milligrams.

and veins were then exposed, and 100 mg of heparin dissolved in 2 cc of physiologic sodium chloride solution was injected intravenously. A cannula was inserted in the left femoral artery, it being connected with a manometer apparatus by means of a short rubber tubing. The tubing contained, under slight pressure, 50 cc of a 3 per cent acacia solution and 10 mg of heparin. Stopcocks, which separated the manometer and cannula from the blood stream of the animal were then released, and a graphic record of the arterial pressure was traced on a smoked drum. At the same time, a roentgenogram was made. This procedure represented the control and is indicated on the graph (Fig 1) as Period I. Consecutive roentgenograms and pressure tracings were made at dif-

ferent stages during the experiment and are recorded with corresponding numerals on the graph. The changes in heart size were estimated by outlining the heart shadow on the roentgenogram with pencil and tracing a silhouette from this on smooth white paper. The silhouettes were carefully cut and weighed, the weight being accurate to 1 mg. The blood pressure variations were determined by the rise and fall of the pressure curve in relation to the base line.

Since the findings and procedures were practically the same in each cat, one experiment will serve as an example for all. Cat H, a male, weighing 4.2 kg., was etherized and prepared for study as outlined in the plan of technic. After the control picture and blood pressure records were made, an amyl nitrite "pearl" was broken and held in a cone over the animal's nose. Following three or four respirations, the blood pressure fell, and a tracing and a roentgenogram were taken immediately. This procedure represents Period II, and it will be seen on comparing the

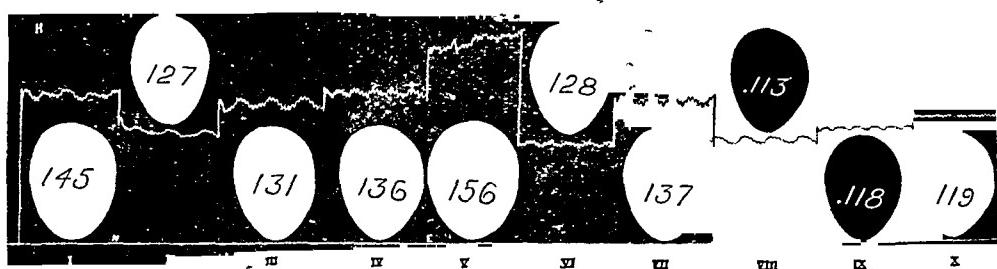


Fig. 2 (Cat E, weight 3.2 kg.)—Left Silhouette of the heart (weight, 558 mg) before bleeding. Right Decrease in the heart silhouette of 148 mg after withdrawal of 28 cc of blood.

silhouettes that there was a diminution in heart size with the corresponding fall in blood pressure. Periods III and IV show the return of the pressure to normal with a gradual increase in the heart shadow. Fifteen minutes after the completion of Period IV, 0.25 cc of a 1:1000 solution of epinephrin was given intravenously. One minute later, the pressure rose, and a picture was taken as the recording needle reached the highest point on the smoked drum. The heart silhouette in this period (V) was markedly increased in size. The pressure dropped rapidly below normal, and after it had become stabilized another tracing and roentgenogram were made (Period VI). Period VII represents a return of the blood pressure to normal with an enlarged heart area as compared to the preceding period (VI). After the pressure had remained constant for fifteen minutes, 40 cc of blood was withdrawn from the left femoral artery. The blood pressure dropped rapidly and was traced at the lowest point. The roentgen-ray silhouette at this time showed a diminution in

heart size Successive tracings and roentgenograms taken at twenty minute intervals show a gradual although incomplete return to normal Quite similar results were obtained in other cats

COMMENT

This experiment suggests the ready adaptability of the heart to changes in the size of the blood vessels It seems that when the vessels are dilated and the pressure is lowered, the heart diminishes in size When the vessels are contracted, the blood pressure is elevated and the heart is increased in size This relationship is expressed in a striking way in Period V when epinephrin was given while the heart was still showing the effects of amyl nitrite by diminished size Here the outline was greatly increased in all dimensions over any previous silhouette The very slight increase of heart size in Periods IX and X (after bleeding) as compared to the marked changes following amyl nitrite administration and the secondary effects of epinephrin are due, no doubt, to the loss of fluid from the vessels as the result of venesection The return to normal is dependent in all probability on the transfusion of fluids from the tissues into the vessel spaces which occurs slowly In this regard Meyer⁴ has shown that the heart of a rabbit after bleeding does not completely return to normal from twelve to twenty-four hours if the animal is placed in the cage without fluids to drink He produced, however, a rapid dilatation of the heart after the intravenous injection of colloidal calcium phosphate We found this to be true in three of the experiments when the heart quickly returned to normal after the injection of a 10 per cent solution of acacia, equal to the amount of blood withdrawn

CONCLUSIONS

- 1 In experiments on cats following the inhalation of amyl nitrite, the heart temporarily decreases in size with a fall in blood pressure
- 2 There is a transient increase in heart size with the rise in blood pressure during the vasoconstricting effect of epinephrin
- 3 Immediately after bleeding, there is a fall in blood pressure and a corresponding diminution in the size of the heart The blood pressure approaches normal within a short time, but the heart remains comparatively small
- 4 There is a suggested relationship between the blood pressure and changes in the heart size

RECTAL DIGITALIS THERAPY*

ROBERT L LEVY, MD

NEW YORK

Not infrequently, patients suffering from heart failure are unable to take digitalis by mouth because of nausea, vomiting or surgical operation. It is in the advanced stages of myocardial insufficiency, at a time when the indications for administering digitalis are most urgent, that nausea and vomiting are often prominent symptoms. The occasional onset of cardiac weakness following operative procedures, when oral medication cannot or should not be resorted to, likewise calls for stimulation of the heart muscle. The margin of safety between therapeutic and toxic dose, when a member of the digitalis group is given by vein, is sufficiently small to render this method of administration hazardous. Concerning the effects of subcutaneous or intramuscular injection, but little definite information is at hand. Such evidence as is available indicates that there is considerable variability in the rate of absorption when digitalis or strophanthin is so given, especially in the presence of circulatory stasis and edema. Furthermore, these substances, being irritants, cause pain when injected into the tissues. The present study was undertaken to ascertain the feasibility of rectal digitalis therapy.

LITERATURE

Only a few fragmentary reports concerning the administration of digitalis by rectum have been recorded. These papers are based largely on clinical impressions. No studies of the rate of absorption have been made.

Eichhorst,¹ in 1916, administered small daily enemas containing digitalis to a group of patients with chronic cardiac insufficiency, and believed that it was in this variety of heart failure rather than in acute decompensation that rectal therapy was indicated. The enema employed, termed by him "mikrolysmia," consisted of 5 cc of lukewarm water, 10 drops of digalen (Cloetta), 10 drops of tincture of strophanthus and 0.3 gm theocin. The enema was given each morning over a relatively long period of time. The usual digitalis effects were noted. Interruption in treatment resulted in recrudescence of symptoms. When evidence of irritation of the large bowel appeared, the addition of from 5 to 10 drops of tincture of opium for two or three days served to do away with the discomfort. Vomiting was observed in a few instances and was

* From the Department of Medicine of the College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital

¹ Eichhorst, H. Die Behandlung chronischer Herzmuskelinsuffizienz, Deutsch Arch f klin Med 118: 337, 1916

attributed to the theocin. Omission of this drug from the enema, or substitution of another diuretic, abolished this undesirable effect. In patients in whom digitalis, given by mouth, had lost its therapeutic action, Eichhorst believed that the rectal method of administration often proved strikingly effectual.

Morin,² following this lead, studied twelve cases in which digitalis was given in the form of suppositories. These contained digalen 1 cc (equivalent to 0.15 gm of digitalis), benzocain and coco butter. He recommended that three suppositories be employed daily for three days, to be followed by two on the fourth day, if necessary. In seven cases, the results were excellent. One patient, though markedly improved after the first course, failed to respond a second time. Four died. All showed characteristic digitalis effects. Morin stated that absorption from the rectum was good, and that the total dosage required for digitalization was identical with the amount required when the drug was given by mouth. In his opinion, the advantage of the rectal method lay in the possibility of administering digitalis to patients who were vomiting. One of the striking results obtained was in a patient with irregular rhythm (probably auricular fibrillation) in whom, prior to medication, the heart rate was 165, the pulse rate, 85. Three days later, after 0.45 gm digitalis had been given, the heart rate was 80, with all the beats felt at the wrist.

Cloetta,³ in a discussion of the various methods of administering digitalis, set forth a number of reasons why, *a priori*, absorption from the rectum should be rapid and quantitative. There is no admixture with hydrochloric acid, which this author believes he has shown destroys the activity of the glucosids and forms a combination which is toxic for the nerve centers. In stasis of the mesenteric veins and liver, the absorption of digitalis by mouth may be uncertain. By the administration of the drug by rectum, the portal system is, in a measure avoided, in that all of the blood from the inferior hemorrhoidal veins and part from the middle hemorrhoids according to this author, goes directly into the inferior vena cava and thence to the heart. Cloetta also expressed the belief that the prevalent conception, which assumes that the dose of a drug given by rectum must be larger than when given by mouth, is erroneous.

The more recent paper by Meyer⁴ adds but little to those just cited. He gave 1 cc of liquid digipuratum in 10 cc of water, in a small

² Morin, J. De l'emploi de la digalene en suppositoires, Rev Med de la Suisse Romande **38** 694, 1918.

³ Cloetta, M. Ueber die Anwendungweise der Digitalispräparate, Corr-Bl f schweiz Aerzte **49** 1193 (Aug 14) 1919.

⁴ Meyer, E. Ueber rectale Digitalistherapie, Klin Wchnschr **1** 57 (Jan 8) 1922.

glycerin enema Like Eichhorst, Meyer believed that patients refractory to digitalis by mouth often responded satisfactorily to the rectal method of treatment

MATERIAL AND METHOD OF STUDY

Digitalis was administered by rectum twenty-six times to twenty patients Cases with fibrillation of the auricles were selected for study, in order that the effect of the drug on the heart rate might be employed as one of the criteria of the rapidity of absorption One case of ectopic auricular tachycardia is included in the series The patients all suffered

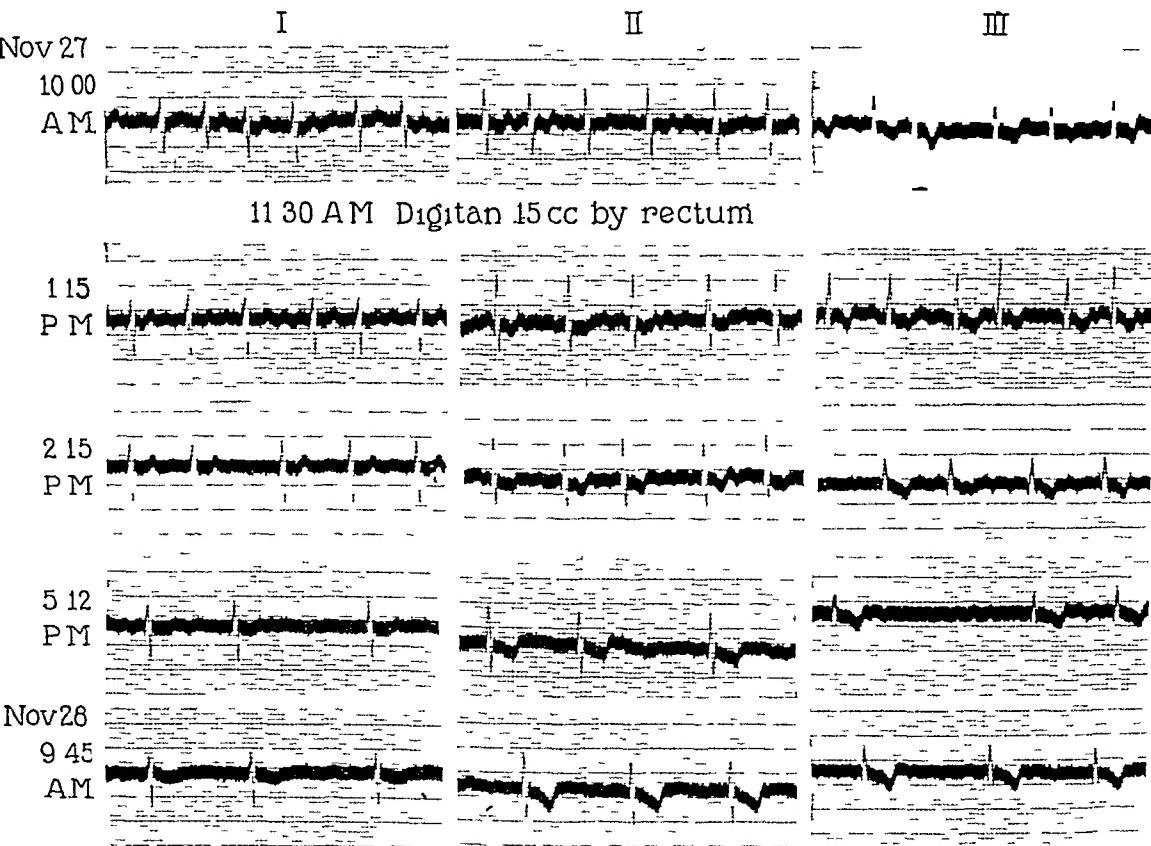


Fig 1 (Case 1) —Electrocardiograms showing auricular fibrillation The ventricular rate, November 27, at 10 a m, was 122, 1 15 p m, 136, 2 15 p m, 100, 5 12 p m, 54, November 28, 9 45 a m, 60 A change in the form of the T-waves is first apparent in the record made at 1 15 p m, when T2 and T3 are more deeply inverted The inversion increases progressively and is most marked, November 28

from heart failure In all, the initial ventricular rate was rapid, usually over 120 a minute The group comprised individuals ranging in age from 9 to 62 years The clinical conditions associated with auricular fibrillation likewise varied Depending on the type and extent of myocardial damage, as well as on the presence or absence of edema, serous effusions, infection, etc , variations in the rapidity and degree of digitalis action were to be anticipated

Some of the patients had received digitalis prior to admission to the hospital, but the amount given was always inadequate to relieve cardiac insufficiency. When the condition of the patient warranted, a preliminary period of several days in bed, without medication, preceded rectal therapy.

After suitable control observations, hourly records of heart and pulse rates were charted for eight hours following the digitalis enema, and at four hour intervals for the next twenty-four hours. In nineteen instances, an electrocardiogram was taken just before administration and approximately every hour thereafter for three, four, or five hours. Another curve was made on the morning following rectal therapy. The electrocardiograms served to check the bedside observations of rate. In addition, they furnished graphic records of alterations in rhythm, when these occurred, and of changes in the form of the T-waves, which are often characteristically altered by administration of digitalis.⁵

PREPARATION EMPLOYED AND TECHNIC OF ADMINISTRATION

The preparation employed was an aqueous solution of purified extract of digitalis leaves called "digitan." One cubic centimeter of the liquid contained the equivalent of 0.1 gm of powdered leaf. Biologic assay was made by the half hour fog method. The solution was put up in sealed glass ampuls, and was sterilized in them by autoclaving. Tests of biologic activity made after one year showed no deterioration. Clinically, there was no evidence of loss of therapeutic potency after the ampuls had been kept for this length of time.

Early in the course of the work, a tincture of digitalis was used. The alcohol was occasionally found to be irritating to the rectal mucosa unless the dose to be given was diluted to such volume that the enema, because of its bulk, was often expelled. No such difficulties were encountered with the use of the aqueous preparation. The digitalis tincture, properly diluted, may be employed for rectal use.

With one exception, the entire dose of digitalis was given at one time. The patient received a preliminary cleansing enema. After evacuation, from 8 to 20 cc of digitan was given by rectal tube and washed through with 25 cc of tap water. A rectal tube of small caliber was inserted to a depth of about 6 inches (15 cm) from the anal orifice. The funnel into which the digitalis was poured was held about 15 inches (37.5 cm) above the level of the anus. After the tap water had been allowed to flow in, the tube was clamped, left *in situ* for fifteen minutes and then slowly withdrawn. The patients were carefully instructed to resist any desire for a bowel movement for at least six hours.

⁵ Cohn, A. E., Fraser, F. R., and Jamieson, R. A. Influence of Digitalis on the T-Wave of the Human Electrocardiogram, *J. Exper. Med.* **21**, 593, 1915.

RESULTS

Rate of Absorption—Retardation in ventricular rate occurred in every instance following digitalis administration (Table 2). As was to be expected, there was commonly coincident diminution in the pulse deficit. The average time necessary for an unmistakable initial effect on rate was two hours and thirty-five minutes⁶. The interval ranged from one hour and fifteen minutes to seven hours and forty minutes. The average time which elapsed before a maximal effect on rate was apparent was nine hours and thirty minutes. This time ranged from

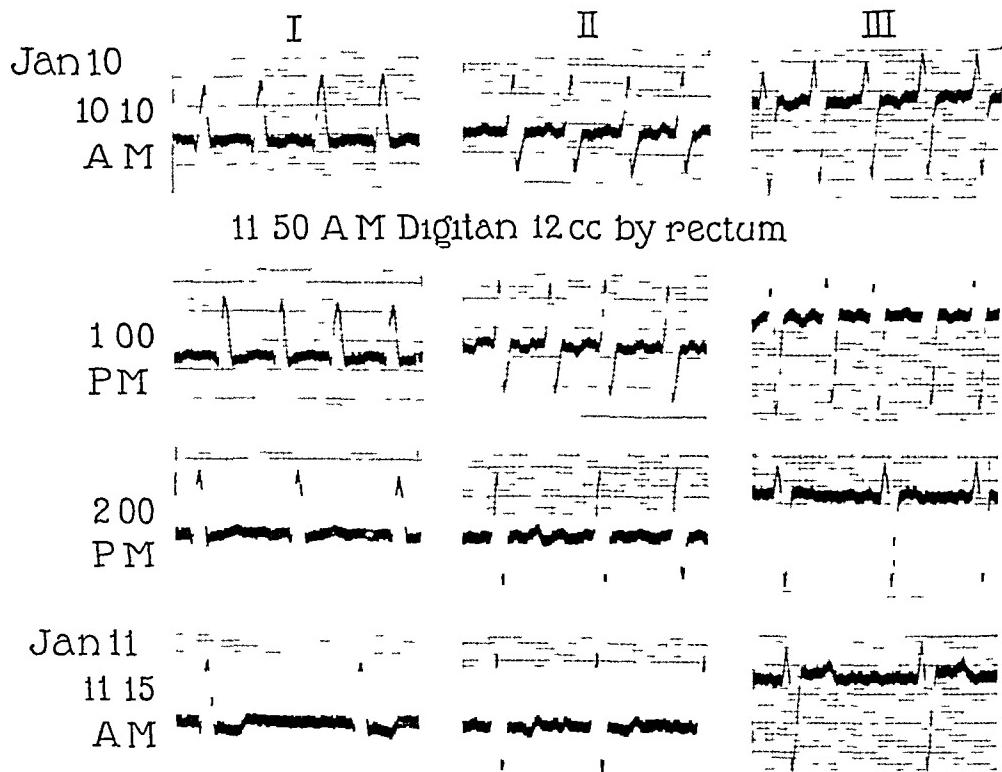


Fig 2 (Case 2)—Electrocardiograms showing auricular fibrillation. The ventricular rate, January 10, at 10 10 a m, was 158, 1 p m, 154, 2 p m, 80, January 11, 11 15 a m, 70. A change in the form of the T-waves is first apparent in the record made at 2 p m, and is more pronounced in the curves taken on the day following rectal therapy.

three hours and fifteen minutes to twenty-two hours (Table 1). It is unnecessary to enter into the clinical details which made inevitable such variations in the time necessary to accomplish the effects observed. Dosage, the degree of decompensation, and the state of the myocardium undoubtedly were cardinal factors which affected the issue. There were probably also individual variations in the rate of absorption.

6 By an unmistakable effect on rate, the beginning of a progressive retardation is meant. This initial fall in rate ranged from 10 to 74 beats, but was, for the most part, from 15 to 30 beats a minute.

A characteristic change in the T-wave of the electrocardiogram occurred in fourteen of the nineteen observations. In five cases, although the rate was slowed, no T-wave change was observed. The initial effect was seen, on an average, in two hours and thirty minutes approximately the time necessary for a beginning fall in rate. This period varied in length from one hour and twenty minutes to five hours and fifteen minutes (Table 1). Usually, a greater change in the T-wave was seen in the curves made on the morning following digitalis administration (Figs. 1 and 2).

It is of interest to compare the rapidity of digitalis action when the drug is administered in large single doses by mouth, with that observed when it is given by rectum. Robinson⁷ studying the effect of massive oral doses of the tincture (from 15 to 25 c.c.) on the heart rate in cases of auricular fibrillation, observed an initial effect in from two to five hours, a maximal effect in from six to twenty-six hours. Eggleston and

TABLE 1.—Summary of Twenty-Six Observations on Twenty Patients

	Time for Initial Effect on Rate	Time for Maximal Effect on Rate	Time for Initial Effect on T Wave*
Average	2 hours, 35 minutes	9 hours, 30 minutes	2 hours, 30 minutes
Range	1 hour, 15 minutes to 7 hours, 40 minutes	3 hours, 15 minutes to 22 hours	1 hour, 20 minutes to 5 hours, 15 minutes

* The T-Wave effect was studied in nineteen instances only. In five instances, no change was observed, although an effect on rate was apparent.

Wyckoff⁸ found significant differences in the rate of absorption of purified and official tinctures. After the oral administration of large doses of purified tincture, calculated by Eggleston's body weight method, definite evidences of action on the heart were noted in from one to three hours (average one hour and fifteen minutes). Full therapeutic effects were seen in from four to twenty-four hours (average, fifteen hours and forty-five minutes). The official tinctures were slower in their action. Cohn and Levy,⁹ after giving powdered leaves in the form of Merck's digitán in cases of auricular fibrillation, observed an initial effect on rate in from one to eleven hours (average, three hours and fifteen minutes), and a maximum effect in from one to eighteen hours (average, nine hours). The T-wave of the electrocardiograms, which was altered in 90 per cent of the cases showed a beginning change in

7 Robinson G C. Rapidity and Persistence of Action of Digitalis on Hearts Showing Auricular Fibrillation. Am J M Sc 159: 121 (Jan) 1920.

8 Eggleston C, and Wyckoff, J. Absorption of Digitalis in Man, Arch Int Med 30: 133 (Aug) 1922.

9 Cohn, A E and Levy, R L. Unpublished data. A preliminary account of this work appeared in the Proceedings of the Society for Experimental Biology and Medicine 17: 81, 1920.

from seven to forty-eight hours (average, twenty-four hours). It is therefore apparent that the lapse of time necessary for the occurrence of initial and maximal effects on the heart rate in patients with auricular fibrillation, when digitalis is given by mouth, closely approximates that required for the occurrence of similar effects when the drug is given by rectum. The T-wave of the electrocardiogram appears to be affected earlier when the drug is given by rectum.

No observations on the duration of effect were made. The patients chosen for study were, for the most part, seriously ill, and it was con-

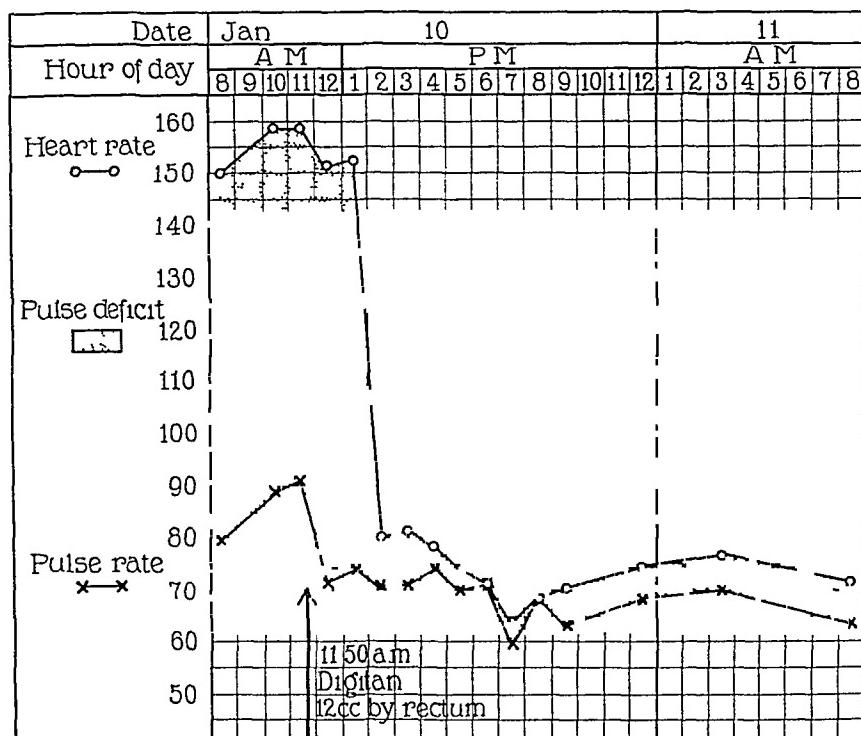


Fig 3 (Case 2)—Clinical chart

sidered desirable to continue the administration of digitalis by mouth as soon as this seemed indicated. Furthermore, as will be pointed out, rectal therapy is to be regarded as an emergency measure. The duration of action is therefore not relevant to the problem.

Clinical Effects—A desirable therapeutic result was apparent in every instance. The usual digitalis effects were observed. In many of the patients, the results were dramatically rapid and beneficial; in others, although there was manifest improvement, further digitalis dosage, by mouth, was necessary to reduce the heart rate to the desired level and to overcome the residual circulatory stasis. In the early stages of the work, relatively small doses of from 8 to 10 cc were employed. Later, larger amounts were given. It was found that a safe and effective dose

for a previously undigitalized adult is 15 c.c., containing the equivalent of 15 gm of powdered leaves. This amount is approximately the same as has been found satisfactory in the use of massive doses of digitalis given by mouth.⁷ The same considerations which indicate modification of the amount given by mouth serve as indications for varying it when given by rectum. It is of particular importance, in this connection, to take into account any digitalis which may have been given to the patient before rectal therapy is undertaken.

In two patients, in whom absorption was especially rapid and in whom, therefore, a brilliant effect on the circulation was achieved, nausea and vomiting following digitalis administration (Cases 1 and 2, Table 2) The doses in the two cases were, respectively, 12 and 15 c.c. There were no other evidences of untoward digitalis action in any of the patients.

Three patients were vomiting and two suffered from severe nausea at the time of rectal therapy. All were acutely decompensated, and medication by mouth would have been difficult or impossible. The nausea and vomiting promptly disappeared with the subsidence of heart failure.

In two cases, digitalis apparently induced an alteration in rhythm. In one, a woman of 56, with mitral stenosis, who had received no digitalis prior to her admission to the hospital, and in whom the signs of heart failure were not conspicuous, normal rhythm followed the administration of 14 c.c. after the lapse of one hour and forty-five minutes. The duration of the auricular fibrillation was not known, but the patient was at rest in bed in the hospital for twenty-four hours before medication was undertaken. The relationship between therapy and change of rhythm seemed reasonably clear.

The second case was that of a girl of 9 who was critically ill with rheumatic fever, mitral stenosis and insufficiency and pericarditis with effusion. She had had no digitalis, but was intensely nauseated. The heart rate suddenly rose to 166. An electrocardiogram showed an ectopic auricular tachycardia. On the following day, as the tachycardia persisted, 10 c.c. of digitoxin was given by rectum. After the lapse of thirteen hours and fifty minutes, normal rhythm, with rate of 106, ensued. Three days later, following an exacerbation of the rheumatic infection and an elevation of temperature to 104 F., the auricular tachycardia recurred. In this case, the relationship between digitalis administration and the change in rhythm was probable, but not definitely established.

In order to illustrate more clearly the variety of clinical effects observed, three cases are herewith briefly cited.

REPORT OF CASES

CASE 2.—A man, aged 56, with syphilis, chronic myocarditis, and auricular fibrillation, had been taking quinidin uninterruptedly for a year, with maintenance of sinus rhythm. About two weeks prior to admission to the hospital, he discontinued the drug, and five days later, he was aware of a recurrence of

TABLE 2—Clinical Summary of Cases

Case	Patient	Age	Clinical Diagnosis*	Amount of Digitalis Given, G.c.	Time for Initial Effect†		Time for Maximum Effect,‡ Hr Min	Heart Rate		Remarks
					Rate Hr Min	Tr-Wave Hr Min		Before Digitalis Given	At Time of Digitalis Effect	
1 J H	31	Mitral stenosis and insufficiency	20	1 30	3 15	18 30	125	65	Vomiting before digitalis was given, entire dose not retained	
2 P O	56	Syphillis, chronic myocarditis	15	2 45	1 45	5 45	122	54	Submitted after rectal digitalis	
3 A N	62	Chronic myocarditis	12	2 10	2 10	5 10	158	75	Vomited after rectal digitalis	
4 J W	14	Rheumatic fever, mitral stenosis and insufficiency, aortic insufficiency	8	2 5	0	11 15	102	114	Partly expelled 1 hour after administration	
5 J S	10	Mitral stenosis and insufficiency, asthma	10	2 10	2 55	4 10	129	88	Died 2 weeks later	
6 E M C	46	Chronic myocarditis, torticollis	6	1 40	?	11 40	130	110	Partly, though incompletely digitized, vomiting	
7 S L	9	Rheumatic fever, mitral stenosis pericardial effusion, auricular fibrillation	12	4 15	0	6 45	110	76	Second dose given 6 hours after the first	
8 F K	51	Mitral stenosis and insufficiency, chronic nephritis	12	1	?	16	110	72		
9 M M C	44	Mitral stenosis and insufficiency	12	2	?	6 10	120	90		
10 E C	40	Mitral stenosis and insufficiency, aortic insufficiency	10	3 15	?	6 15	108	96		
11 S S	42	Mitral stenosis and insufficiency	12	2 15	0	14 15	126	82		
12 D B	51	Syphillis, myocarditis, hypertension	12	5	5 15	5	122	78		
13 A P	39	Mitral stenosis and insufficiency	8	2 15	2 15	7 15	130	72		
14 M C	56	Chronic myocarditis, hypertension	14	4 45	?	11 45	118	110		
15 P G	59	Arteriosclerosis, chronic myocarditis, hydrothorax	12	1 30	1 40	11 30	132	108		
16 L G	59	Mitral stenosis and insufficiency	10	1 30	?	3 45	120	90		
17 M F	42	Mitral stenosis and insufficiency	14	1 20	3 30	3 30	139	83		
18 A W	48	Mitral stenosis and insufficiency	18	2 5	0	22	110	80		
19 B D	56	Mitral stenosis	14	1 45	1 45	1 50	110	128		
20 K H	52	Chronic myocarditis, hypertension	15	1 50	6 35	168	168	76	Rhythm changed to normal Paroxysmal fibrillation, regular rhythm returned 4 days later	

* In all cases except Case 7 there was auricular fibrillation

† Time is recorded in hours and minutes

fibrillation He attempted to continue at work, but shortness of breath and palpitation forced him to seek medical attention He took no medicine of any sort before coming to the hospital On admission, the heart rate was from 150 to 160, with 80 beats coming through to the wrist After twenty-four hours in bed, during which the heart rate and pulse deficit remained at about the same levels, he was given 12 cc of digitan by rectum Two hours and ten minutes later, the heart rate was 80, the pulse deficit but 8 (Figs 2 and 3) The maximum effect was apparent seven hours and ten minutes after administration, when the heart rate was 72, with no pulse deficit Absorption in this case was unusually rapid The curves shown in Figure 1, taken from another patient, also show a strikingly rapid effect These two patients were the only ones who suffered from nausea and vomiting after rectal digitalis therapy

CASE 10—A woman, aged 40, with mitral stenosis and insufficiency, aortic insufficiency and auricular fibrillation, was admitted to the hospital with advanced heart failure She had taken no digitalis for eight days, but was badly nauseated The heart rate ranged from 126 to 140, the pulse rate from 116 to 122 a minute The temperature varied from 101 to 103 F At 1 45 p m on the day following admission to the hospital, 12 cc of digitan was given by rectum (Fig 4) An initial retardation in rate was apparent in one hour and forty-five minutes, and the T-wave first altered its form at about the same time There was a gradual, progressive fall in heart rate during the next fifteen hours On the following morning at 8 o'clock, the heart rate was 84, with 78 beats felt at the wrist The temperature fell to normal coincidently with the subsidence of heart failure, and there was no recurrence of fever

This case furnishes a striking example of a variety of pyrexia associated with cardiac decompensation, which disappears with reestablishment of an adequate circulation The slower therapeutic effect in this patient may have been due, in a measure, to the extreme degree of failure which existed at the time digitalis was given

CASE 4—A boy, aged 14, with subacute rheumatic fever, mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation, and a greatly hypertrophied heart, had been under observation in the hospital for many months Although continuously digitalized, there was always some degree of heart failure, which necessitated keeping him in bed March 13, the oral administration of digitalis was temporarily discontinued At this time, the heart rate ranged from 76 to 88, with little or no pulse deficit March 16, the ventricular rate began to rise During the next ten days, he was given small amounts of digitalis by mouth He complained of pains in the small joints of the hands

March 28, the temperature was 101 2 F The apex rate was 160, the radial rate, 124 The patient was orthopneic and cyanotic, and he complained of precordial pain and cough There were râles at both lung bases The liver was 4 cm below the costal margin There was no edema Digitalis, 0 6 gm, was given by mouth

March 29, the boy appeared to be moribund He was pale, gasping for breath and irrational at times The heart rate ranged from 160 to 166 The precordial pain, cough and moist râles at the bases of the lungs were more marked than on the preceding day He vomited several times after coughing, and was unable to retain medicine by mouth Intravenous injection of strophanthin seemed unwise because of the fairly large amounts of digitalis which had recently been given At 11 50 a m, 10 cc of digitan was given by rectum (Fig 5) By 2 p m (two hours and ten minutes later), the heart rate had fallen from 160 to 116, with a corresponding fall in pulse rate At 4 p m, the ventricular rate was 110, but by 6 o'clock, it had again risen to 130 At this time, however, there was great symptomatic relief At 6 20 p m, 6 cc of

digitán was given by rectum. There was a gradual retardation of ventricular rate during the night, and by 6 o'clock the following morning, the heart rate was 86, with no pulse deficit. He slept nearly all night. The temperature, which had been 101.8 F fell to 99 F. From this time on, improvement was continuous. Daily doses of digitalis by mouth were begun. May 18, the boy began to walk. He was discharged from the hospital, July 22.

In this case, rectal digitalis therapy was unquestionably responsible for the saving of life.

Digitalis has been given, by rectum, to twelve patients following surgical operation, in whom signs of cardiac weakness were apparent. Because of vomiting or on account of operations on the upper gastrointestinal tract, oral medication was impossible. In all, a satisfactory

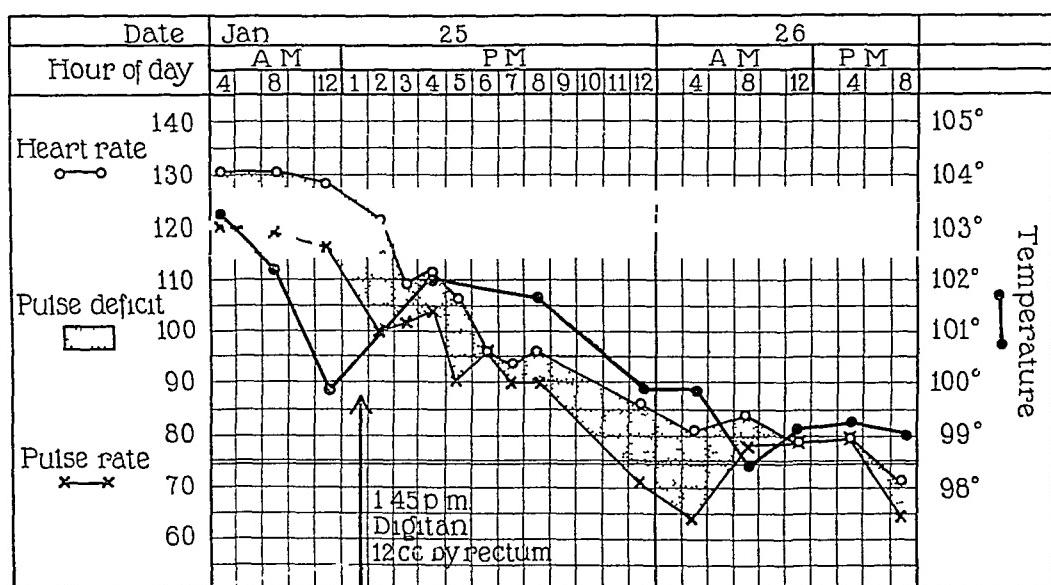


Fig. 4 (Case 10) — Clinical chart

effect was evident, as measured by ordinary clinical criteria. Accurate graphic control was not employed, nor could the effect on rate be studied, as normal (sinus) rhythm was present in every instance. The studies in the cases of fibrillation, however, permit of the assumption, by analogy, that the drug was absorbed and that whatever beneficial effects were to be anticipated from digitalis under the circumstances, were obtained.

COMMENT

Absorption from the Rectum —As Cloetta³ has pointed out, there are *a priori* reasons for believing that the absorption of digitalis from the rectum should be good and its action on the heart relatively rapid. It is profitable, in this connection, to consider briefly the anatomy and venous blood supply of the rectum.

The rectum is from 12.5 to 15 cm in length. It is sacculated, usually presenting, when distended, three dilatations, of which the lowest and largest, called the *ampulla*, may measure 25 cm or more, in circumference. This forms a pouch having a relatively large capacity. The rectum has a fairly rich venous blood supply, composed of two plexuses, one internal, lying in the submucosa, another external, resting upon its outer surface. The internal plexus opens partly, at the anal orifice, into the branches of the inferior hemorrhoidal veins, and partly, by branches which traverse the muscular coats, into the external plexus. The latter has three sets of efferent veins: (1) the inferior hemorrhoidals, which empty into the internal pudic, and thence, by way of the internal iliac, into the inferior vena cava; (2) the middle hemorrhoidals, comparatively large veins, which open into the internal iliac or one of its tributaries, and thence into the inferior vena cava, and (3) the superior hemorrhoidals, which empty by way of the inferior mesenteric, into the portal vein.

It is thus apparent that most of the blood from approximately the lower two-thirds of the rectum finds its way directly into the inferior vena cava and to the heart, without going through the portal system and the liver. The introduction of digitalis into the lower rectum may, therefore, reasonably be compared to a slow intravenous injection. It is with this idea in mind that rectal therapy has been advocated in cases of congestive heart failure, when stasis in the splanchnic vessels and swelling of the liver may render absorption from the upper gastrointestinal tract relatively slow.

Two considerations raise the question as to whether this concept is valid from the standpoint of clinical therapeutics. First, the lower two thirds of the rectum is only 3 or 4 inches (7.5 or 10 cm.) in length, and second, the rate of absorption of digitalis when given by rectum, as has already been pointed out, approximates closely that observed when the drug is given by mouth. It was therefore deemed important to determine from what portion of the lower intestinal tract absorption takes place when fluid is introduced into the rectum according to the technic previously outlined. The following simple experiments furnished an answer to this question.

To four convalescent ward patients, 20 cc of a 15 per cent solution of sodium iodid was given by rectal tube and was washed through with 25 cc of water, the technic employed being identical with that used in administering digitalis. Fifteen minutes after injection of the iodid, and again approximately two, four and six hours later, roentgenograms of the abdomen were made. The iodid solution, which is similar to that used in pyelography, casts a shadow clearly visible in the roentgenograms.

In three of the patients, some of the solution, immediately after it had been given, was visible in the rectum, but it was for the most part in the lower sigmoid (Fig 6) In two of these instances, some of the iodid could be seen in the descending colon as high up as the splenic flexure In the fourth case, all of the iodid was in the sigmoid In three cases, all of the shadow had entirely disappeared in from four to six hours In the fourth patient, a considerable amount of the solution was still present in the sigmoid and upper rectum five hours after it had been given It is thus apparent that, given in the manner described, iodid solution introduced into the rectum remains for the most part in

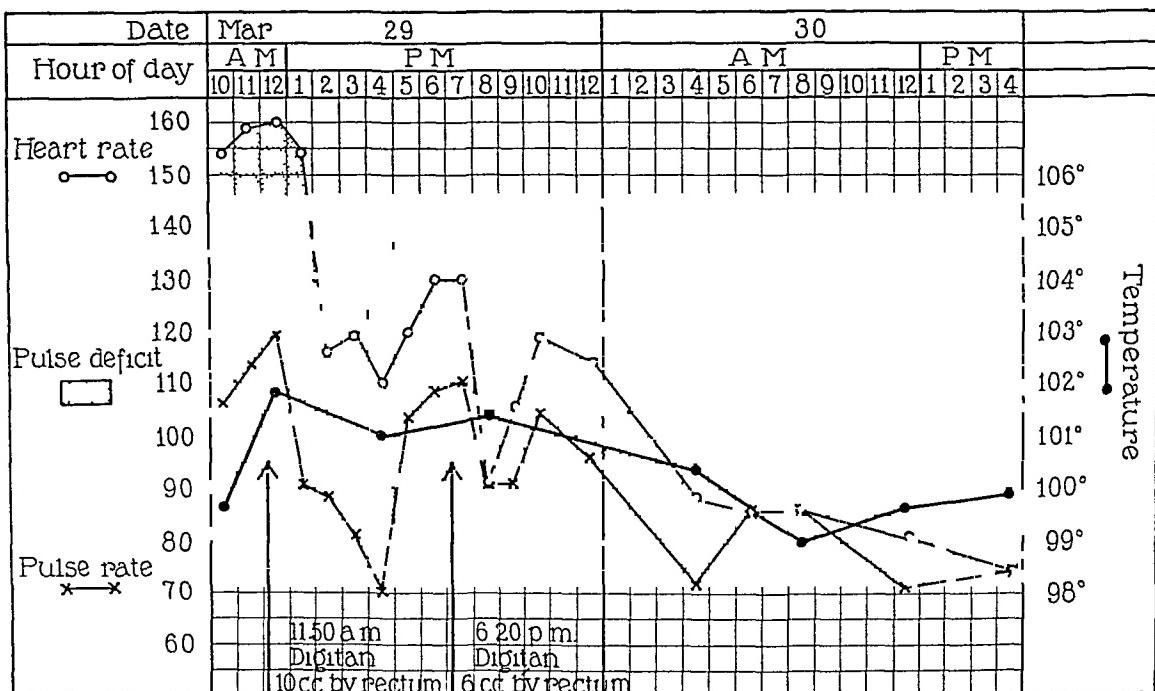


Fig 5 (Case 4) —Clinical chart

the sigmoid flexure and is absorbed in from four to six hours The amount absorbed from the rectum is a small fraction of the amount introduced

Iodid solution was next given to two other patients in order to determine whether, by employing smaller amounts of fluid and giving more attention to the details of the injection, the liquid could be prevented from going beyond the rectum A small caliber tube was inserted for a distance of about $2\frac{1}{2}$ inches (6.3 cm) beyond the sphincter ani and 15 c.c. of iodid solution was washed through with 15 c.c. of water, with the minimum head of pressure necessary to insure flow Again, although some of the fluid was seen in the rectum, most of it had gone into the distal loops of the sigmoid As before, absorption was complete in from four to five hours

These results may be interpreted as indicating that, even with the exercise of reasonable care in introducing such an amount of fluid into the rectum, most of it finds its way at once into the lower loops of the sigmoid and is absorbed from this portion of the intestine. A relatively small amount remains in the upper portion of the rectum and an even smaller quantity is absorbed from that part drained by veins which empty directly into the inferior vena cava. It is clear, then, that digitalis, given by rectum, is taken into the venous circulation for the most part via the mesenteric and portal systems. Hence, it is not surprising to

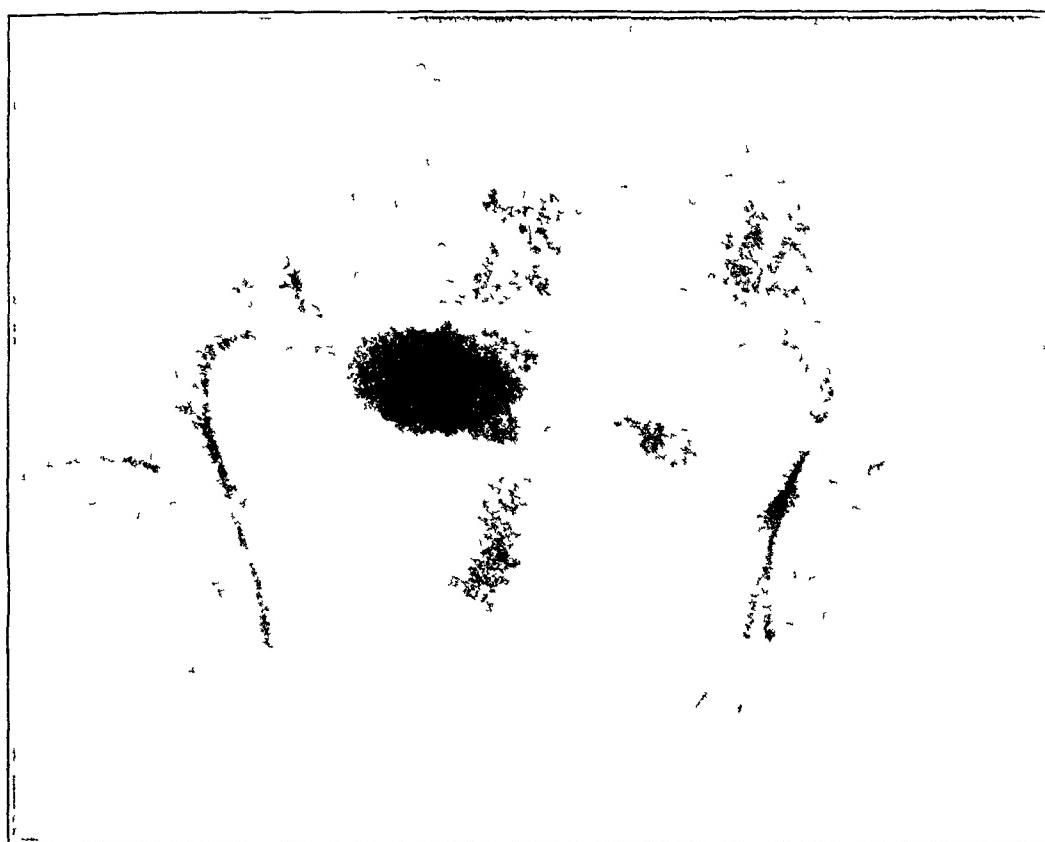


Fig. 6.—Roentgenogram of the lower abdomen twenty-five minutes after administration of 20 cc of a 15 per cent solution of sodium iodid by rectum. The iodid solution was washed through the rectal tube with 25 cc of tap water. The entire 45 cc was retained and is seen in the rectum and lower sigmoid.

find that the rate of its absorption, as measured by its effects on the heart, is quite comparable to that observed when similar doses are given by mouth.

The Place of Rectal Digitalis Therapy in the Treatment of Heart Failure.—When it is possible to give digitalis by mouth, this method of administration is unquestionably the one of choice. Its simplicity, safety and efficacy recommend it. If sufficiently large doses are given, a beginning effect on the heart may be obtained in from two to five hours, a maximal effect in from six to twenty-four hours. Experience justifies

the statement that if a failing heart will respond to digitalis at all, it will react favorably when the drug is given by mouth, provided a potent, absorbable preparation is given in adequate amounts. In those rare emergencies when immediate cardiac stimulation seems imperative, it may be desirable to resort to the intravenous injection of strophanthin.

Rectal digitalis therapy has its field of usefulness, not in supplanting, but in supplementing the oral method of administration. It is to be regarded as an emergency measure, to be used particularly in the presence of nausea or vomiting, or after surgical operation, when oral medication is not feasible. As it has been shown by Hatcher and Weiss¹⁰ that nausea and vomiting, as symptoms of digitalis intoxication, are reflex effects through the direct action of the drug on the heart and are not due to local irritation in the stomach or intestine, similar symptoms may occasionally be anticipated and have, indeed, been observed after rectal administration. The dose of digitalis when given by rectum has been found to be comparable to that employed when a large, single dose is administered by mouth.

SUMMARY

1 Digitalis was administered by rectum twenty-six times to nineteen patients with auricular fibrillation and to one patient with ectopic auricular tachycardia. It has also been given in twelve surgical cases following operation.

2 The preparation employed was an aqueous solution of a purified extract of digitalis leaves. One cubic centimeter contained the equivalent of 0.1 gm of powdered leaf.

3 The amounts given ranged from 8 to 20 cc. With one exception, the total dose was administered at one time.

4 The average time necessary for an unmistakable initial effect on rate was two hours and thirty-five minutes. The average time which elapsed before a maximal effect on rate was apparent was nine hours and thirty minutes. A characteristic change in the T-wave of the electrocardiogram occurred in fourteen of nineteen observations. The initial effect was seen, on an average, in two hours and thirty minutes.

5 A desirable therapeutic effect was apparent in every instance. In many of the patients, the results were dramatically rapid and beneficial.

6 Employing a solution of sodium iodid, which casts a shadow in a roentgenogram, it has been shown that fluid introduced into the rectum finds its way, for the most part, into the distal loops of the sigmoid and is absorbed from this portion of the intestine. A small proportion is

¹⁰ Hatcher, R. A., and Weiss, S. Seat of the Emetic Action of the Digitalis Bodies, Arch Int Med 29: 690 (May) 1922.

absorbed from the lower rectum. Most of the digitalis given by rectum reaches the heart via the mesenteric and portal veins and not by way of the inferior vena cava.

7 Rectal digitalis therapy is intended to supplement, not supplant, the oral method of administration. It is useful in the presence of nausea and vomiting, or after surgical operation, when oral medication is not feasible. The dose is comparable to that employed when a large single dose is given by mouth.

DIFFERENTIAL IMPROVEMENTS IN THE SYMPTOMS OF TOXIC GOITER DURING ROENTGEN-RAY TREATMENT AND REST *

MARGARETE M KUNDE, PH D
CHICAGO

The value of the basal metabolic rate as an index of the degree of toxicity in goiter has been fully discussed by Du Bois,¹ Means,² McCasky,³ Boothby⁴ and others. The influence of roentgen-ray treatment on the symptoms of toxic goiter appears to be variable. Halsted⁵ (1914) states that selected cases of exophthalmic goiter show improvement after treating the thymus gland with roentgen ray. Seymour⁶ (1916) briefly reports the effect of roentgen-ray treatment in eighty cases of exophthalmic goiter. All but seven of these patients showed marked improvement. Seymour concludes that the pulse rate is nearly always reduced at once, and that an increase in the body weight, improvement in nervous symptoms and tremors and a change in the size and condition of the thyroid gland occur almost immediately. Means and Aub² (1919) report on a group of fifteen cases of exophthalmic goiter treated with roentgen ray in which the patients received treatments in varying amounts over a period of from two to three years. This group as a whole showed progressive improvement as measured in terms of the basal metabolic rate. The average metabolism of the group before the treatment was 63 per cent plus. From two to three years after the treatment, it had been reduced to 13 per cent plus, and all of the patients were leading normal lives. These authors conclude that, in the majority of cases, the results after from two to three years are as good with roentgen ray as with surgery, and that after surgery, the metabolism shows a rapid preliminary fall and a secondary rise followed by a final fall, and that, with roentgen-ray treatment, there is a progressive fall. Also that the rest factor is not so important with the roentgen-ray treatment, and there are practically no fatalities. The

* From the Hull Physiological Laboratory of the University of Chicago

1 Du Bois, E F Clinical Calorimetry, Arch Int Med **17** 915 (June) 1916

2 Means, J H, and Aub, J C Basal Metabolism in Exophthalmic Goiter, Arch Int Med **24** 645 (Dec) 1919

3 McCasky, G W Basal Metabolism Determinations in General Internal Diagnosis, J A M A **74** 927 (April 3) 1920

4 Boothby, W M Basal Metabolic Rate in Hyperthyroidism, J A M A **77** 252 (July 23) 1921

5 Halsted Harvey lectures, 1913-1914, p 224

6 Seymour, M Boston M & S **175** 568 (Oct 19) 1916

patients treated surgically get along better and the risk of operation is less if they have previously had the thyroid and thymus glands irradiated.

In a later publication (1923), Means and Holmes⁷ review the history of the use of roentgen-ray treatment in exophthalmic goiter, and report on fifty-eight new cases treated with roentgen-ray. These authors also discuss the method of treatment and the difficulty in accurately measuring the dosage. Forty-four of the fifty-eight new cases were exophthalmic goiter. Of these patients, sixteen showed little or no improve-

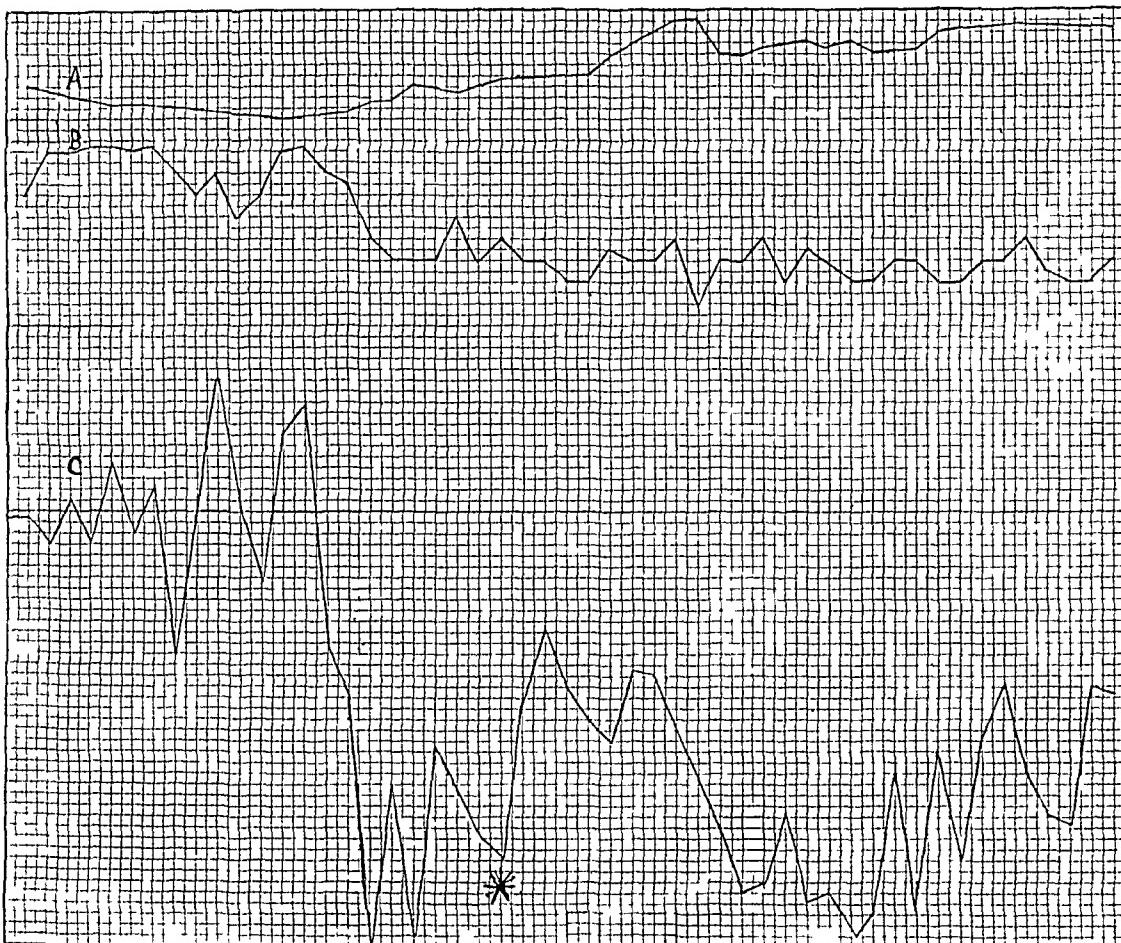


Fig 1.—Changes in body weight, pulse rate and basal metabolism from June 5, 1921, to Dec 11, 1923. *A*, body weight in kilograms, *B*, pulse rate per minute, *C*, number of calories of heat produced every twenty-four hours. Discontinuation of roentgen-ray treatment is indicated by a star.

ment, twelve were cured and sixteen showed some improvement. No patient was made worse by the treatment. Fourteen of the new cases were toxic adenomas. All of these patients showed improvement and five were completely cured. In the toxic adenoma cases, the drop in the pulse rate and basal metabolism, and the gain in body weight were more gradual as the result of the roentgen-ray treatment than in the exoph-

⁷ Means, J. H., and Holmes, G. W. Roentgen-Ray Treatment of Toxic Goiter, Arch Int Med 31:303 (March) 1923.

thalmic goiter cases. The authors also state that nine of the cases reported in the 1919 series were still under observation. Six of these patients have normal metabolic rates from five to six years after their first treatment. Another shows an elevation of 6 per cent. Means concludes that the beneficial effects of roentgen rays should be obvious during the first four or five months of treatment and that it seems that the roentgen ray is a useful therapeutic agent in the treatment of toxic goiter.

The case here reported is unique in that the patient's basal metabolism was watched more closely during the period over which roentgen-ray treatments were given than any case previously reported. The basal metabolism of the patient was determined indirectly by means of the Benedict portable respiratory apparatus. The graphic method was used to determine the amount of oxygen consumed. The determinations were



Fig 2.—Region subjected to irradiation Left anterior, right posterior

made between 7 and 8 in the morning. A normal individual of the same age, weight, height and sex should have produced 1,665 calories of heat every twenty-four hours.⁸ May 21, 1922, the patient ate no food until noon, so that two metabolism determinations were made one at 7:00 a.m., the other just before noon. The test made just before noon was 7 per cent higher than the test made at 7:00 a.m.

TABLE 1.—Roentgen-Ray Treatment of Patient C C C *

Date	Region	MAM	Date	Region	MAM
11/29/21	1-3-5	27	5/12/22	1-2	30
12/1/21	2-4-6	27	5/12/22	1-2	30
12/20/21	1-3-5	27	5/9/22	1-2	30
12/22/21	2-4-6	27	6/12/22	1-2	30
1/10/22	1	30	6/28/22	1-2	30
	3-5	27	7/14/22	1-2	30
1/12/22	2	30	8/1/22	1-2	30
	4-6	27	8/22/22	1-2	30
1/31/22	1	30	10/25/22	1-2	42
	3-5	27	11/8/22	1-2	36
2/2/22	2	30	11/22/22	1-2	36
	4-6	27	12/9/22	1-2	36
2/21/22	1-2	30			

* C C C was the patient of J. L. Miller, M.D. The roentgen ray treatments were given by H. E. Potter, M.D., to whom I am indebted for the data. In all the roentgen ray treatments, the filter was 3 mm of aluminum and 1 thickness of sole leather, the distance, 10", spark gap, 8.

From the tables it can be seen that the highest metabolism occurred, May 19, 1922. At that time the rate was 48 per cent above the normal. Under roentgen-ray treatment and rest, the rate was reduced so that on August 4, it was only 18.6 per cent above the normal. From Aug. 15, 1922 to June 8, 1923, there was a steady increase in the basal metabolism despite the fact that during this time much roentgen-ray treatment was given, as can be seen from Table 1. The effect of the roentgen ray on the metabolism seemed stimulating rather than depressing. The rate reached a level of 28 per cent above the normal, but the body weight increased, the pulse rate decreased, and there was a marked improvement in the exophthalmus and other nervous symptoms. From June 8,

TABLE 2.—Metabolism, Body Weight and Pulse Rate

Date	Calories of Heat per 24 Hrs	Pulse	Weight, Kg	Date	Calories of Heat per 24 Hrs	Pulse	Weight, Kg
6/ 5/21	2,325			3/25/22	2,170	80	69.0
5/ 9/22	2,324	96	68.0	3/26/22	2,189	80	69.0
5/10/22	2,302	104		4/ 4/22	2,118	86	71.0
5/11/22	2,340	104		4/22/22	2,184	84	72.2
5/12/22	2,307	105		5/ 26/22	2,180	84	73.0
5/14/22	2,376	105	66.4	6/ 8/22	1,969	88	74.0
5/15/22	2,310	104		7/19/22	1,920	76	74.2
5/16/22	2,355	105	66.2	9/11/22	2,040	84	71.0
5/17/22	2,199	100		9/12/22	1,974	84	70.9
5/18/22	2,293	96		9/13/22	1,980	88	71.5
5/19/22	2,462	100	65.8	9/14/22	2,057	80	72.0
5/20/22	2,337	92		9/15/22	1,967	86	72.0
5/21/22	2,265	96		9/16/22	1,970	84	71.8
5/23/22	2,403	104	65.0	9/17/22	1,935	80	72.2
5/26/22	2,428	105		9/18/22	1,953	80	71.2
6/ 6/22	2,206	100		9/19/22	2,094	84	71.2
7/24/22	2,159	88	65.6	9/20/22	1,954	84	71.5
8/ 4/22	1,924	88	66.4	11/24/22	2,112	80	73.0
8/ 9/22	1,951	84	66.6	12/ 3/22	2,015	80	73.5
8/11/22	1,933	84		12/ 4/22	2,121	84	73.5
8/15/22	2,110	84	67.2	12/ 5/22	2,173	84	73.6
8/23/22	2,078	92		12/ 7/22	2,093	88	73.7
8/30/22	2,033	84	67.6	12/ 8/22	2,052	82	73.6
10/22/22	2,012	88	68.7	12/ 9/22	2,046	80	73.6
1/14/23	2,156	84	69.0	12/10/22	2,073	80	73.3
3/ 5/23	2,223	84		12/11/22	2,065	84	73.3

to July 19, 1923, there is again a depression, resulting in a basal metabolic rate which averaged only 12 per cent above the normal. No more tests were made until September 11. At this time, there was a slight increase in basal metabolic rate, with a loss of 5 pounds (2.2 kg.) in body weight. From September 11, to December 11 the metabolism again increased so that it stood 21 per cent above the normal, but the symptoms of toxic goiter have all practically disappeared.

These improvements may not be due to the roentgen-ray treatments alone since the patient had been at complete rest for more than nine months before any of the symptoms of toxicity began to subside. Spontaneous remissions equally, or even more, marked have been reported to occur in exophthalmic goiter when the patients were merely on a rest

treatment and that not nearly so complete or prolonged as in this case.⁹ The therapeutic value of roentgen-ray treatment in toxic goiter cannot be estimated until more is known in regard to the cause of the symptom complex in this disease. Too much emphasis, no doubt, has been placed on the increased basal metabolism which usually is found in this disease. The basal metabolic rate does not always run parallel with the symptoms of toxicity. In this case, the low metabolism occurred between July 24 and August 11, 1922. After that, excepting for a short period in the summer of 1923 (June 8 to July 19), there has been a constant average increase of 13 per cent. The marked amelioration in the eye symptoms, tremors, tachycardia and body weight has occurred since August 11, 1922, in spite of this increase in metabolism. Repeated irradiation since August 11 has not resulted in a further reduction of the metabolic rate or an ability to maintain it at the lowest level in the course of the treatment.

The most interesting phase of this closely studied case of toxic goiter is the fact that, during the last year, the goiter has been reduced in size, the body weight has increased 15 pounds (6.8 kg.), and the tremors, tachycardia and exophthalmos have been markedly reduced in spite of the fact that the basal metabolic rate has actually increased, so that at the end of the observations it was 21 per cent plus. The patient is clinically much improved, despite the high basal metabolism. In this case, the symptoms of toxicity do not run parallel with the basal metabolic rate.

⁹ Kessel, Leo, Hyman, H. T., and Lande, Herman. A Study of Fifty Consecutive Cases of Exophthalmic Goiter, *Arch. Int. Med.* **31** 433 (March) 1923.

THE HUMAN THORAX CONSIDERED AS A RESONATOR

G E BUSHNELL, M D
Colonel U S Army, Retired
PASADENA, CALIF

Disturbance of the particles of any elastic body may result in the production of sound waves. The pitch of the sound will depend chiefly on the elasticity of the body and on its mass. When the body consists of a volume of air confined within elastic walls and under the pressure of the atmosphere, its elasticity may be considered to be constant. In this case the pitch of its proper, or fundamental tone is determined by the volume of the contained air if one of the dimensions of the cavity does not greatly exceed the others. In tubes, the diameter remaining unchanged, the pitch of the fundamental tone is determined chiefly by the length of the tube, the longer the tube, the lower the pitch.

The resonator of the physicist is an apparatus used for the analysis of sounds into their component tones. The ideally perfect resonator answers only when a tone of a single definite pitch is sounded before it, the pitch being that of the fundamental tone of the volume of air contained within the resonator. But practically all resonators especially, according to Giesswein,¹ soft-walled resonators, respond to tones other than their fundamental tone. If response is strong to tones nearly of the pitch of their fundamental tone, there is said to be a zone of resonance. When an air space, or other sounding body, vibrates with the production of its proper tone the vibrations are called free vibrations. Vibrations induced in a resonator which are not of the frequency of the fundamental tone are said to be forced on it. Forced vibrations are of much importance in musical instruments. A flat and thin piece of wood, or a stretched membrane, has vibrations of its own proper periodicity, but these are not obtrusive and the structure is so brittle that it responds readily to tones of widely varying pitch. The sound of a tuning-fork, for example, is reinforced when the fork is set on a flat-topped, wooden table. The reinforcement is greater when the sounding surface overlies an air space. The combination is then called a resonance chamber. The sounding board of the piano with the air within the case is a resonance chamber.

The violin is a still more conspicuous illustration of a resonance chamber, in which tones of a wide range are imparted to the air within the body. The greatest pains are taken by the maker to obtain the most

¹ Giesswein Ueber Brustresonanz, Verhandl d Gesell deutsch Hals-, Nasen- u Ohrenärzte, 1921, p 87

vibratile wood, and a form of instrument has been evolved empirically which is not only capable of producing strong and rich tones, but also of responding well to tones of widely varying pitch. It is manifestly necessary that the violin shall not act as a resonator, that is, that it shall not especially reinforce the fundamental tone of its cavity. The f-shaped slits in the upper surface and the hollows in the sides are said to have for their purpose the prevention of resonator action. The tones of the strings are, then, forced on the violin body, the extraordinarily sensitive wood of which controls the vibrations of the air within, so that the fundamental tone with its free vibrations does not differ noticeably in strength from the forced vibrations of other tones.

But, even in stringed instruments, the volume of the air space cannot be left altogether out of consideration for it governs the range of the vibrations that can be forced on it. So we find that the violin, viola, violoncello and bass viol, while they are all instruments of a wide range of tones, differ in the size of their air volumes, as well as in the length of their strings, high-pitched tones are more easily forced on a relatively small volume of air, very low-pitched tones can only be forced on larger volumes.

Tones may be forced on a resonator in two ways. First, a tone not of its proper frequency may be forced on a resonator to supplant altogether its fundamental tone. An example of this may be found in the reed pipe of the organ. In this kind of a pipe the generator of the resonator action of the pipe is the vibrations of an elastic tongue of metal, called the reed. Such vibrations of a definite frequency and furnished abundant energy by a strong blast of air, influencing, as they do, the air within the pipe to move to-and-fro in a regular way, may succeed in causing the resonator to sound with a tone not of its proper rate of vibration. Practically, this amounts to causing the pipe to be out of tune. The tuner is therefore obliged to tune the reed pipe at the reed as well as at the pipe, whereas, in the case of the flue pipe he needs only to regulate the tone of the pipe.

The second way in which vibrations are forced on a resonator is to cause it to sound to tones not of its proper frequency, in addition to its normal response to its fundamental tone. The resonator has then a zone of resonance. Natural resonators are usually of an improper shape, so that their walls and air volume cannot vibrate fully and entirely even at their normal rate. In cavities, like that of the packing box, in which one diameter exceeds the others to a certain extent as a rule, the long diameter is of importance in determining the pitch of the tone. We may readily see that if the cavity of the resonator is irregular there may be several diameters so nearly of the length of the principal diameter that tones corresponding to them may be heard when mixed vibrations generate sound. This will be particularly true when the generator submits

a noise for resonator action. When a resonator has a zone of resonance under such circumstances, such of the tones of its response as are not of the pitch of its fundamental tone may be said to be forced on it, the important distinction from the first class of forced tones is that the fundamental tone is not affected in pitch by them.

In general, volumes of air confined within elastic walls react most strongly to imparted vibrations by their free vibrations. Vibrations of other periodicities may be forced on a volume of air but only to any considerable extent when they approximate the normal rate of vibration of the cavity, unless the walls are specially constructed to be sensitive to a wide range of sound and the cavity they enclose is shaped accordingly.

A wooden box, covered, or placed bottom up, when struck emits a noise that is a combination of a variety of individual tones. Predominating among the tones of the noise we hear one of relatively low pitch, as compared with the other tones, which is the fundamental tone of the volume of air confined within the box. Given a series of empty wooden boxes of the same general construction, but varying in size, a blind man with a hammer could determine the relative size of each box because the law of response by the fundamental tone is immutable, and the pitch of this tone under the assumed conditions will vary with the size of the box.

The determination of the mode of production of the fundamental tone of the struck wooden box, of the percussed thorax and of the flue pipe of the organ is complicated by the fact that in the cases of the box and of the thorax a concussion is imparted to the contained air, and that in the case of the flue organ pipe a blast of air produces vibrations of the lip of the tube. In these three cases the air volumes do not, properly speaking, function as resonators because the vibrations which excite their proper response simply furnish energy which enables the air to originate its own proper vibrations, in other words, the air is not necessarily excited by communicated vibrations of its own periodicity.

The behavior of the wooden box as a resonator when excited by musical tones may be tested by a simple experiment. Holding a hand saw by the handle in a vertical position, strike the center of the blade with a piece of metal. A sound is produced which is evidently composed of a number of tones of a metallic quality. Lower the saw so that one corner of the lower end of the blade rests on an empty wooden box and exercise sufficient downward pressure so that the blade bends slightly and strike it again. The sound is now of shorter duration, but one of the tones becomes louder and has a "wooden" quality. Repeat this with several boxes and the same result will be obtained, but the pitch of the reinforced tone will vary with the size of the box, boxes smaller than the one first used having higher-pitched, larger boxes lower-pitched.

tones. Here a bent sawblade, percussed lightly in a direction perpendicular to its long diameter, can hardly be said to communicate a gross concussion to the box.

When the vibrating saw comes in contact with the box cover the sound waves of the blade, if they do not happen to coincide in periodicity with the free vibrations of the air volume of the box, are forced to a greater or less degree on it. This air volume, being now conjoined with a different vibrating system, is forced to vibrate at a rate which is not that of its normal vibration, the two systems reacting on one another and a tone resulting therefrom which might be called a compromise between the normal vibrations of each, but the pitch of the resonator tone is usually less affected than that of the tone of the generator.

Now, if a single tone had been forced on the boxes, the result would probably be a loud response from one box, less strong responses from larger and smaller boxes of nearly the same size and a feeble response from boxes differing considerably in size. In this case the forcing of tones on the box would be analogous to the forcing of the tones of phonation on the human thorax. For, in the case of the latter a musical tone can only be forced effectively on it when the frequency of the tone is the same, or nearly the same, as that of the fundamental tone of the thorax.

But in the experiment described, instead of a single tone, we have a complex of many tones of varying pitch. The responses of the different boxes, within limits, seems to be about the same, as respects loudness, but the pitch of the predominant tone varies with the size of the box. We must therefore suppose that the individual boxes select different tones for resonance, that, in other words, the reinforcement by each box is that of a tone which lies within the zone of resonance of that particular resonator. We may say therefore that the volume of air of the box governs to a very considerable extent even in the case of well marked musical tones, as it does in the case of communicated concussions. There is an obvious analogy here with the resonance of the thorax which produces the vesicular murmur, as we know it, except that the fact that the vesicular murmur is of the same pitch as that of the percussion note encourages the belief that the larynx, as a generator, does not force the tone on the larynx, but submits vibrations to it which are of its own proper periodicity, so that the response is made by its free vibrations. But in addition to the fundamental tone, since vesicular breathing is a noise, other relatively weak tones which lie within the zone of resonance of the thorax must also be forced on it, so that vesicular breathing furnishes an example of forced vibrations of the second class.

The wooden box so much resembles the thorax, as an acoustic apparatus, that Martini² uses the former in his studies of the problems of thoracic sound. The laws set forth with regard to boxes may therefore properly be applied to the thorax. The thorax resonator, however, presents some peculiarities which should be noted. The air cavity of the thorax, like a cushion stuffed with horsehair, is multilocular, solid substances break up the continuity of the volume of the air without, however, preventing it from vibrating as a unit. The normal thorax differs from all other resonators in two respects. First, the solid parts of its contents are largely under a certain definite tension, secondly, it is what might be called a compound resonator. There is the resonator of which the contents, broadly speaking, are represented by the total volume of the air cells, and within this resonator is situated a system of air tubes which is also a resonator but one of a smaller volume, the fundamental tone of which is necessarily of a higher pitch. The proper contents of the larger resonator, having a deep toned fundamental tone, are not adapted to vibrate with the frequency of the air within the bronchial tree. So far, therefore, as vibrations which escape from the bronchi are not of the periodicity of the tone of the larger resonator they are more or less completely damped by the air cells. We may say, then, that in the thorax we have a large resonator in which is contained a small resonator surrounded by insulating material. The insulation varies in thickness and, conformably to that fact, we find that bronchial sounds which are almost entirely excluded in some parts of the lungs, in other parts are forced to a greater or less extent on the air cells and so are transmitted to our ears. The note of percussion is noticeably higher over the upper thorax where bronchial tubes are thinly covered, than it is over the lower thorax where the insulating structures have a greater thickness. In one part of the air tube system, the trachea, there is no insulation and accordingly percussion of this tube gives tympanitic resonance—the fundamental tone of the cavity.

In percussion of the normal thorax the note is composed of quite high tones from the impact of the blow on the pleximeter, moderately high tones from the vibration of the chest wall and also from the resonance of the bronchial system and the deep tones of thoracic resonance. The vibrability of the chest wall may be expected to be practically the same at all points of its surface which are not covered by thick muscles, and its note should therefore be the same. If we find higher pitched tones over the upper thorax than near the base of the lung, we may ascribe the greater prominence of high pitched tones over the upper lung, so far as they do not signify disease, to the normally

² Martini, Paul. Studien über Perkussion und Auskultation, Deutsch Arch f klin Med 139 65 (April) 1922

better conduction of sound from the bronchi of the latter region Practically, in percussion we learn to disregard the pleximeter tones and the tones of the wall, as being constants, and to concentrate our attention on two classes of sound from the lung, the low pitched chest resonance and the group of higher pitched tones

Martini found the percussion note of the exenterated and inflated lung to be of the same pitch as that of the thoracic note before removal of the lung The tones of the chest wall are not therefore forced on the lung in such a way as to modify its fundamental tone This would not be expected if the thorax acts as a resonator, and the fact that they are not is one of the proofs that this is the case But if the walls of a resonator do not control the vibrations of the air volume they must be controlled by those vibrations The vibrations of the wall must be the same as the vibrations of the cavity, however they may have originated, and this is as true of the forced vibrations of concussion as it is of the free vibrations that cause the fundamental tone The drumlike chest wall can conduct very high pitched tones, but so far as it serves as the container of an air volume it is dominated by that volume It can be shown by a simple experiment that high pitched tones are not forced on the lung Press a finger firmly against the ear over the auditory meatus, and percuss the part of the finger that lies directly over the meatus with a finger of the other hand The impact of skin against skin produces loud and high pitched sounds These disappear if the finger is in the least removed from actual contact with the ear, thus showing that these very high tones have not sufficient energy to survive, as sound, the transition to the air When the finger is pressed against the chest wall in percussion these tones are lost in the louder and deeper tones, but they are nevertheless still present, for Selling³ found that resonators answered to the high tones of the pleximeter in finger on finger percussion But though the solid acoustic media of the chest wall are capable of carrying them around the chest, they are not to be heard posteriorly when percussion is made anteriorly, therefore the vibrations of these sounds not only originate locally in the disturbance of the equilibrium of the skin particles immediately involved, but remain localized in the sense that the lung does not vibrate in response as a resonator Such vibrations as may be communicated to the lung, if they are reinforced by it, receive only a local reinforcement from air cells directly implicated in the concussion, not a reinforcement of the air cells acting as the content of a resonator, and the lung does not allow the chest wall to vibrate in response to them, as the wall of a resonator

This interpretation is substantiated by the phenomena of coin percussion The familiar coin test in pneumothorax is based on the prin-

³ Selling Deutsch Arch f klin Med 90 163, 1907

ciple that normal lung tissue prevents the chest wall from transmitting vibrations which the latter is able to transmit when not in contact with lung tissue. As is well known, if a silver coin is laid on the chest and percussed with another coin of the same metal, in pneumothorax the "silvery" sound is carried through the chest and may be heard distinctly over the back when percussion is made anteriorly. This test is distinctive of pneumothorax for the reason that it disappears in the case of the normal lung. The lower tones of the sound are indeed audible, but the very high pitched silvery sound is not. Now, the success of the experiment in pneumothorax shows that the failure to transmit the silvery sound in health is not to be ascribed to the chest wall. It might be supposed that since, as shown in pneumothorax, the chest wall can transmit the silvery sound, this sound would be carried around the chest without passing through the normal lung and should be heard by the observer who listens behind, which we know is not the case. The explanation is furnished by the observations of Jacobson and Danielopolu,⁴ who found that when percussion is made over the absolute heart dulness, or the liver, and the second observer auscultates behind just below the level of the normal lung the silvery sound is to be heard. Here the conduction is effected through airless organs, the heart and liver. The observation shows that the thoracic wall is abundantly able to transmit the silvery sound in health, so far as its own vibrations are concerned, but there wherever it is in contact with the lung it acts as the wall of a resonator and cannot therefore vibrate to high pitched tones to which its contents are deaf. At the same time, the lung tissue which is sometimes spoken of as sluggish conducts lower pitched tones so well that the slightest sound of percussion can be heard through it with ease. The lung is a very sensitive resonator for sounds within its range, a fact which is shown in its response to weak tones furnished by the lynx.

We may think of the relation of the chest wall to the lung in percussion as follows. Heterogeneous vibrations from the blow are communicated from the pleximeter to the chest wall and necessarily disturb the equilibrium of the parts struck. Rapid vibrations pass readily through the wall. But the lung is in close contact with it. Such vibrations when they reach the air cells disturb their equilibrium also, but the elasticity of the lung tissue does not permit its particles to fly back and forth in the tempo indicated. They are forced to move but they move slowly. The rapid vibrations when they meet such an obstacle are therefore in part reflected soon after penetration, producing sound waves in the localized reflections to a small extent, and thus effecting a certain reinforcement of the high pitched tones, but for the most part dying out. The chest wall vibrates to the sound waves returned from the lung, as well as to those which pass through its own tissues without

⁴ Jacobson and Danielopolu Munchen Med Wchnschr 59 216, 1912

penetrating the lung, but acoustically speaking, it forms practically a part of the lung so that when vibrations of the two classes, the autochthonous vibrations of the chest wall and the sound waves of the lung, pass outward in all directions from the point of impact to the other portions of the wall everywhere they encounter the resistance of the underlying lung and die out. Under the conditions the walls cannot institute independent vibrations of the periodicity required for high pitched sounds because they are everywhere damped by the lung. The rapid vibrations have had little effect so far as the lung is concerned, except perhaps to furnish some energy by the disturbances which they have created. Slow vibrations, on the other hand, are not so well adapted to the normal vibrability of the wall as those which are rapid, but nevertheless are transmitted well to the lung, the structure of which permits them to pass freely, and, undergoing reflection, they produce stationary sound waves which fit from the outset the dimensions of the cavity or may be forced to adapt themselves to it. The result is a loud fundamental tone which we speak of as the reinforcement, or resonance, of the tone furnished by the resonator. What has happened, however, is in reality that the energy of a series, or several series of vibrations which in the unfavorable acoustic medium of the generator (in this case the pleximeter) could not be effectively applied is able when the vibrations reach a favorable medium to develop itself to the best advantage, so that what is perhaps a small part of the total energy of the blow creates a sound which is enormously greater than all of the other sounds of percussion.

Martini⁵ criticises my⁶ statement that "the sound of percussion, as it reaches the lung, contains the (its) fundamental note." This statement requires farther amplification in order to be understood. A blow on the bare chest—immediate percussion—a blow on a noiseless pleximeter of soft rubber (Selling) and blows on various other pleximeters, including the finger, laid on the chest differ as to the sounds of impact of the blow which are high pitched disharmonic partials of greater or less obtrusiveness, according to the nature of the substances that clash. But all these variations in the manner of exciting the proper vibrations of the air volume of the thorax make no difference in the pitch of the resulting tone.

A very considerable part of the energy of the blow of immediate percussion is converted into heat and friction, on account of the soft and yielding character of the skin and other soft parts of the chest wall. A stronger blow is therefore required in immediate than in mediate per-

5 Martini, P. The Mechanism of Production of Breath Sounds, Arch Int Med 32:313 (Sept) 1923.

6 Bushnell, G E. The Mode of Production of the So-Called Vesicular Murmur of Respiration J A M A 77:2104 (Dec 31) 1921.

cussion to produce the same effect. The function of the pleximeter is to compress and fix, in part also to push apart the soft parts and, usually to furnish a more or less plane or convex, surface to receive the blow in place of the yielding concavity of the uncovered intercostal space. When pressed firmly against the chest wall the proper vibrations of the pleximeter are so damped that they may be disregarded. Practically, the pleximeter has become a part of the chest wall, viewed as an apparatus for the transmission of sound and the percussion note as we hear it, is the fundamental tone of the thorax plus the sound of impact. For the same reason the hammer, or the hand, which strikes the chest wall directly is for the moment of contact a part of the same apparatus. Now we can interpret this process, as Geigel does, and say that all that the percussion blow furnishes is energy, the lung answering to the commotion of its parts in the only way in which it can answer effectively by its proper vibrations. This is the simplest way of conveying the rôle of the lung in the production of the note of percussion and is sufficiently correct for all practical purposes. But strictly speaking, the vibrations of the chest wall antedate those of the underlying lung. What are those vibrations? They are the only vibrations possible for the wall of a resonator, the vibrations proper to the cavity which it bounds. Therefore, speaking of the effective vibrations and admitting the existence of the vibrations peculiar to the mass of the pleximeter, we may say that the energy of the blow is converted immediately in the chest wall and in the pleximeter into the vibrations of the fundamental tone of the hemithorax. In this sense my statement is believed to be correct.

Martini's² experiments show clearly that disparate vibrations cannot be forced to any noteworthy extent on such a resonator as a wooden box. At the same time, Martini exaggerates the independence of the two systems, box wall and box cavity, because the tone that connects them, the fundamental tone of the cavity is not, and from the nature of the case cannot be, clearly identified in the vibrations of the wall. There is nothing to emphasize vibrations of this frequency among the numerous other vibrations of the wall (or plate) when tested alone. When however, the resonator is excited to action by the same vibrations the sound waves of wall and air react on one another, each strengthening the other, they become one sound which the registering apparatus cannot connect with the wall. Martini speaks of forcing vibrations on the box whereas I believe the vibrations which are of importance in physical diagnosis are the free vibrations which call forth the fundamental tone. The vibrations forced on the lung from the bronchi are not of course imitated in Martini's experiments.

I have never been of the opinion as stated by Martini that the vibrations of the bronchial system are the excitant of the vesicular murmur, if by the phrase Martini means that the fundamental tone of the

bronchial system is forced on the thorax to the exclusion of the proper tone of the latter. It would be quite improbable that a weak and "almost musical" note of considerably higher pitch than that of the thorax resonator should act as the excitant of its fundamental tone. But, in addition to the fundamental tone of the bronchi, a number, perhaps very many, of other tones are present, for bronchial breathing is a noise. Besides their function as a resonator, the air tubes also play a part as speaking tubes down which are conducted the various kinds of laryngeal sounds. No sound waves can pass through an elastic tube without imparting vibrations to it, but these, if differing much in pitch from the fundamental tone, are of little consequence. It, therefore, would not be far removed from the truth to consider the air tubes of the bronchial system, in their relation to vibrations of the frequency of the fundamental tone of the thorax to act simply as the transmitters of such vibrations. As in percussion, so also in breathing, the sounds which are reinforced to become the vesicular murmur are not forced on the thorax but excite its free vibrations. It may be pointed out in this connection that the fact is recognized that the vesicular murmur may be distinguished in the breath sounds, as heard in tracheal breathing (von Muller⁷). It is therefore conducted through tubes, the vibrations of which have a very different frequency from that of its own vibrations, and there should be nothing in the way of the assumption that vibrations of the same frequency reach the lung by passing through the bronchi from the larynx.

I am entirely in accord with the opinion of Martini that "the bronchial breathing which is audible over solidified tissue may rightly be considered as a correctly propagated specific vibration of the air of the bronchial system"⁸. Of course moisture in diseased tubes may effect changes in the sounds of bronchial breathing in the direction of roughened breathing and of musical, sonorous and other râles, but in general Martini's statement is undoubtedly correct. It is to be hoped that the adoption of Martini's standpoint will do away with the more or less absurd theories as to the effect of diseased tissue in modifying locally the character of the breath sounds that pass through it.

7 von Muller, F. Verhandl d deutsch Kongr f inn Med 28 184, 1911, Ztsch f arztl Fortbild 9 417, 1912

8 Martini criticises with some justice my statement that "in massive consolidations of any kind the deep and medium pitched tones are suppressed." I had in mind especially the extreme cases of massive consolidation, in which, according to some authorities there is very little transmission of sound and also the statement of Muller⁷ (first reference) that in pronounced bronchophony only the highest tones of the voice are audible. This author also remarks in the same paper that in pure bronchial breathing the deep tones of the large and small octaves disappear entirely. My remark was therefore not without some justification (Martini himself states in his paper in the *Deutsches Archiv* that the lower border of resonance in most cases of bronchial

Martini attacks Sahli's view that the vocal cords act like the reeds of an organ pipe to produce sounds which arouse the resonator action of the bronchi. I agree with Martini in excluding the action of the smallest bronchi and bronchioles which Sahli believes to act as resonators. But air tubes of a sufficient diameter to permit resonance cannot any more escape acting as resonators of tones of a suitable frequency than can other volumes of air enclosed within elastic walls. My experiments show that tracheal breathing disappears when the larynx is widely opened.

Martini's objection that the vocal cords are too relaxed to be able to stimulate the air current to such loud sounds as those of bronchial breathing would have weight if in order to functionate as reeds it were necessary that the cords should be tense throughout their entire mass, as in phonation. They are indeed too lax to produce musical tones but their relaxation is precisely what favors the production of noises. Their edges flutter in the air current because they are not tense, and in so doing produce the variety of incongruent tones which we call a noise. The sound is produced in a way similar to that of a wet handkerchief exposed to a gale of wind, one edge of the cloth being held tense between the hands and the opposite edge being free to vibrate. The fact that the sounds of laryngeal breathing do not rise in pitch with increase in force of the air current, so long as the position of the cords, their tension and the shape of the mouth and lips remain the same, is rightly held by Geigel⁹ to prove that they undergo resonance. To this argument Martini objects, on the grounds that tracheal breathing resembles, as to its mechanism, what he calls a lip pipe rather than a reed pipe. He then goes on to set forth the properties, as a musical instrument, of a lip pipe. It appears from his exposition that the tones of such a pipe are created by blowing against a sharp edge, the pitch of the tones varying directly with the rapidity, or pressure, of the air. But, he says, these vibrations do not control the fundamental tone of the pipe which is determined chiefly by the dimensions of the cylindrical cavity connected with the lip or orifice. He then goes on to say that the air current is nevertheless

breathing lies at from 574 to 322 vibrations per second), but it was an error to make so sweeping a statement in a condensed presentation of the subject. The sentence preceding the one quoted by Martini justifies his belief that I hold that the tones of bronchial breathing are chiefly resonated in the mouth and nasopharynx. I am unable to explain my carelessness in the wording of that sentence. What I really believe, however, is shown in the preceding paragraph in which I state that "in bronchial breathing the bronchi are the resonators." Martini assumes that I think that resonance is only produced in the bronchi in disease. But I say that the bronchi function in the same way in normal breathing, and my later remark that "the conduction, not the mode of production, of these sounds is changed in disease" should make my meaning clear.

⁹ Geigel, R. *Leitfaden der diagnostischen Akustik*, Stuttgart, Ferdinand Enke, 1908.

of influence on the tone because, with moderate pressure there arises the fundamental tone, with strong pressure the first overtone, finally even the second, etc., are produced, yet, even to cause the first overtone (the octave) much greater differences in intensity of air pressure are necessary than are ever attained in respiration. This behavior of the lip pipe, we may remark, is precisely the same in principle as that of the reed pipe which with much increased force of the air blast may be made to produce the octave of the fundamental tone and other higher overtones. The lip pipe, as Martini describes it, is substantially a resonator. And it is a resonator like the reed pipe and the human air tubes, for in all three the fundamental tone of the cavity dominates under ordinary conditions. The fact that its tones may be changed under high pressure is immaterial in this connection. What we are solely concerned with are the facts relating to weak noises produced by an air current of very moderate velocity. The chief difference between the standpoints of Martini and of myself, then, really is that Martini thinks that the representative of the lip of the lip pipe is to be found in the edges of the bronchial bifurcations within the lungs and not at the larynx. As I have shown experimentally, Martini is probably right in his supposition that edge tones may be produced in the way that he suggests, for in "reciprocating breathing" with closed glottis sounds are heard which resemble the vesicular murmur, as to pitch. But these are produced under positive pressure. This discussion will serve to emphasize the important point that the claims of the writer, as to the origin of the vesicular murmur apply solely to its production under normal conditions, as respects rate of breathing and position of the vocal cords. I have never held that the resonance of the thorax could not be aroused by other excitants than the vibrations of the vocal cords. In fact, the chief reason why my standpoint is not more readily adopted is thought to be the failure of other investigators to realize how easily sounds can be produced within the air tract, and how little specific the sound which excites the resonance of the thorax needs to be.

It must be that the thorax functionates as a resonator because it responds to excitations of various kinds with the same note, a note which varies in pitch with the size of the thorax, but is always of the same pitch in the individual thoraces, and because the cavity controls the vibrations of the walls. Another proof that the thorax is a resonator is afforded by the fact that the musical tones of phonation can only be forced on the thorax when they are of nearly the same frequency as that of its normal vibrations, they are forced the more successfully the nearer they approximate that rate. This shows that the thorax has a zone of resonance for musical tones. But the most important proof that the thorax functionates as a resonator is its relations to the sounds produced by the vocal cords. A resonator, except when struck cannot

create sound. It is dependent on a generator for the origination of the sound and only responds to certain tones by reinforcement. It follows, of course, that if the generator is silent the resonator will also be silent. If then the vocal cords act as a generator for the thorax, acting as a resonator, suppression of their vibrations should result in the absence of thoracic sound. On appeal to experiment this is found to be the case. I was able to abolish not only laryngeal (and tracheal) sounds, but also the vesicular murmur and other breath sounds, as heard over the chest, by opening the larynx wide.

To this argument Maître opposes negative evidence, he always hears breath sounds over the trachea, as well as over the lungs, "when the respiration is rapid enough." Great increase in rapidity of breathing not only makes it more difficult to keep the larynx open, but may possibly cause sound in a new way. Beau¹⁰ states that if the respirations are increased above forty-five per minute a sound is produced from the movement of air through the larynx, though the glottis be wide open. But of course one cannot study the vesicular murmur with such a high rate of respiration. If Maître means what might be called only a normal rapidity of respiration, it might be inquired whether this observer has practiced correctly the difficult art of keeping the larynx open? My method has not been mastered until one has learned to cause all laryngeal sound to disappear from the breathing, as controlled by self auscultation, the bell of a binaural stethoscope being applied to the side of the experimenter's larynx. When the glottis is wide open my experience shows that, the larynx being silent, the lung is also silent, provided of course that adventitious sounds of mouth or nose are also excluded. On the other hand, when the larynx continues to produce sound of any kind, that sound, as modified by the chest resonance, has been audible over the lung. Those observers who have participated in the experiment have expected, and I have exacted it of myself that all sound shall be absent from the lung, otherwise the experiment has been considered to have failed on the particular trial. It may be a question whether so thorough elimination of sound is necessary to prove the point. Laryngeal sound may persist and yet the true vesicular murmur may be absent. One of the acutest of the observers noted this fact. When I remarked, after an experiment had ended, that I had failed during a series of respirations to eliminate all sound, he replied "a sound was to be heard, but it was plainly not the vesicular murmur." It is probably true that the elements of the laryngeal noise which are of the pitch of the fundamental note, being of the deepest tones of the noise, are best, or only, produced when the edges of the vocal cords in their full length are free to flutter. The minimal projection of a part

¹⁰ Beau, J. H. S. Quoted by Bushnell, G. E. *The Discoverer of the Mode of Production of Breath Sounds*, J. A. M. A. 80 895 (March 31) 1923.

of the vocal cords at the time when the cords are not only under a certain tension but are also very closely appressed to the sides of the larynx might therefore very well fail to permit vibrations sufficiently low pitched to call forth the fundamental tone. However, if the above is correct it is difficult to understand why such sounds are audible through the lung.

The production of sound in tubes is easily illustrated. Remove one of the tubes of a binaural stethoscope and blow through it. With forcible blowing the sound at the free end of the tube is loud. But if one breathes through the tube a sound is produced which is louder when the air is sucked in than when it is expelled and, in fact, imitates to a singular degree the breath sounds, as heard over the chest, in that the sound of inspiration is louder and more prolonged than that of expiration.

Martini inquires "Where else should the bronchial breathing originate after the elimination of the vocal cords through a smooth tube, such as the tracheoscope, if not in the tracheobronchial ramifications?" The answer manifestly is "At the upper end of the tracheoscope." And the correctness of this reply would not necessarily be affected, even though it should be shown that respiration through the free tube does not produce audible sound when tested. For, when in place in the larynx it is in a resonator, more than that, in a complicated system of resonators, and slight vibrations would be powerfully reinforced. So that if Martini hears bronchial breathing over the trachea and the vesicular murmur over the chest when the tracheoscope excludes the vocal cords, the explanation is that the high pitched tones of the tube sounds are resonated in the trachea and the larger bronchi, very likely also, the highest of them, in the cavities of the mouth and nasopharynx. This gives an imitation of bronchial, or tracheal breathing. Over the chest the higher pitched tones are suppressed and only the lower tones receive resonance, this imitates the vesicular murmur. In fact, it would be correct to say that it reproduces the vesicular murmur. For there is nothing specific about the series of vibrations in a noise which are of the periodicity of the thorax. The specificity of the sound of the vesicular murmur is due to resonance within the thorax of the tone of the proper pitch, not to the sound as originally made. It is probable that noises produced in a great variety of ways contain vibrations of the proper periodicity for exciting the fundamental tone of the thorax, if introduced through an open glottis, or a tracheoscope during the respiratory movements.

Beau¹¹ called attention to the fact that to avoid producing sound in blowing through a tube, its internal diameter must be at least equal to

11 Beau, J H S. *Traité expérimental et clinique d'auscultation, appliquée à l'étude des maladies du poumon et du cœur*, Paris, 1856.

that of the trachea, which is, he says, about 2 cm. And Baas many years ago published his experiments in producing sound by blowing through a tube. I can only express astonishment that later writers have ignored the obvious application of these facts to sounds which simulate breath sounds when the vocal cords are excluded.

Another source of sound due to escape of air from a small tube to a larger tube or space should be considered in this connection, sounds caused by the respiratory current of air, as it emerges from the nostrils, or passes through nearly closed lips, as well as those caused by slight relaxations of the soft palate. In practice, the auscultator is watchful to prevent such adventitious sounds. They usually mislead by exaggerating the bronchial element of respiratory sound, but there is no reason why they might not also act as excitants of the vesicular murmur, or its equivalent, when the vocal cords are excluded from action. Experiments with the tracheoscope and the like are of no value, unless the observer takes extreme pains to guard against error from this source. When the mode of formation of the vesicular murmur is studied, the subject should always be required to open the mouth widely and to avoid relaxation of the velum palati.

Martini² has demonstrated the fact that the percussion note of the lung, inflated to the physiologic degree, is not dependent on the size of the volume of contained air, as is true of the relaxed lung, finding that two lungs fitted snugly together in a box give no lower tone than one of them alone and that good sized portions of an inflated lung shut off from the remainder of the organ by clamping (but remaining inflated) have a note of the same pitch as that of the inflated lung as a whole.

This demonstration of the specific vibrability of lung tissue is one of the most important contributions to the knowledge of the acoustics of the lung that have ever been made. It explains certain facts in percussion of the chest, and in the auscultation of breath sounds which were formerly inexplicable. At the same time, the discovery does not affect the standing of observed facts, the new doctrine must be reconciled with what is already objectively determined. It will be necessary therefore to consider more particularly the structure of the thorax and its peculiarities as a resonator in the light of Martini's experiments.

Hitherto it has been assumed, for the sake of brevity, that the thoracic cage functionates under the same laws as resonators which are filled only with air. The fundamental law that confined volumes of air under atmospheric pressure will respond to imparted vibrations by free vibrations, the periodicity of which is determined chiefly by their volumes, undoubtedly applies to the thorax. But its structure introduces special conditions that modify this law. Resonators, as a rule, have more or less homogeneous and continuous walls which vibrate as a whole in harmony with their undivided contents. But the con-

struction of the thorax tends to prevent the communication to one of its halves of the vibrations of the other half, and to prevent also the full and free communication of localized concussions to the whole of even one half. The construction, in short, may be said to have in view chiefly the prevention, so far as possible, of the evil effects of shock.

Of thoracic structures the ribs are most exposed to the localized concussion of blows and falls. The bone of the rib is firm, but elastic enough to yield to a certain degree. The articulations with the spinal column and the costal cartilages break the continuity of vibrations. Such vibrations as are carried through these articulations, already damped in front by passing through a heterogeneous sound medium, the costal cartilages, encounter the sternum, a combination of bone and cartilage, which tends to disperse them and, lower down, the connections of the costal arch in part damp the vibrations, in part distribute them to adjoining ribs. The hoops of this part of the thoracic barrel are incomplete, not surrounding the entire circumference. Posteriorly, the structure of the spine with its disks of cartilage prevents free dissemination of vibrations up and down the spinal column, the articulation of each rib with two vertebrae halves the effect of vibrations traveling along individual ribs, with a halving also of vibrations which have passed through a vertebra to the ribs of the other side. Vibrations are also damped by the structures of the mediastinum, for the most part elastic and movable tubes and cavities, and by solid, yet movable organs which constitute the base of the thorax. The two lungs are, moreover, nowhere in actual contact with each other. The general principle of construction is to erect nowhere absolute barriers and to permit vibrations to pass everywhere, but, at the same time, to minimize their violence by reflecting them in many ways and at many places. We may say, therefore, that vibrations of the hemithorax are not communicated readily to the other hemithorax and that it is not to be expected that the two hemithoraces will vibrate freely in unison from concussion imparted to one of them. The results of percussion are such as are to be expected from the anatomic structure. If the undivided thorax vibrated as a resonator, the sound of percussion would be heard equally well over both of its halves, but we do not dream of listening to its note on the other side, and even on the same side the vibrations are often not generalized so far as our perceptions are concerned. Practically, in percussion it is the hemithorax, not the thorax as a whole, that functionates as a resonator.

What is true of the whole thorax is true also of its halves, viewed as independent acoustic units. The anatomic structure of the hemithorax is adapted, not to facilitate vibration of its several portions as a whole to communicate concussions, but on the contrary to prevent to a

considerable degree shocks imparted to one portion from being communicated to other portions

The sound of percussion over the anterior surface of the hemithorax is not heard loudest over the back on the same horizontal level, that is, after passing through the thorax on the shortest line, but higher up and in the same intercostal space. According to Martini,¹² bronchial breathing is propagated farthest from its place of greatest intensity along a rib that cuts this place, less upward and downward in other intercostal spaces. These observations show that, while the sound of the lightest percussion is to be heard over the entire chest posteriorly, a very considerable part of the vibrations pass to the nearest ribs and by them are conveyed upward and backward in their course around the lung. The vibrations of concussion of the anterior thorax are therefore largely conducted away from the base of the upper lobe and do not reach the lower lobe in their full force at all. Posteriorly, a concussion is carried downward as well as forward through the predominating influence of the ribs and reaches the anterior lobe, if at all, near its base where the energy of the vibrations is dissipated along the costal border and such vibrations as penetrate the lung are damped by solid organs.

The disposition of the lung lobes tends to the same end. They are separate from one another, except at the roots of the lung and are surrounded by a lubricated membrane, the arrangement, like a joint, checking the free passage of vibrations. The upper lobe is alone implicated by a blow in front, the lower lobe, except near the summit of the lung, is alone implicated by blows from the rear. It may be said, in general, that the arrangement of the pulmonary lobes is calculated to shield, as far as may be, one lobe from full participation in concussions imparted to another lobe.

The percussion stroke, then, tends to be localized in its effects, the blow must be heavy to bring out the full thoracic resonance, yet the tone elicited by a light blow is the fundamental tone of the thorax. Martini's doctrine of the specificity of the vibrations of lung tissue must be accepted, not only because it is the result of careful experimentation, but also because it alone can reconcile observed facts.

In discussing this theory farther, it will be necessary to consider the properties of the lung as a vibratile organ. In complete pneumothorax the cavity has a tympanitic note if the air is not under positive pressure, with moderate pressure the note is dull tympanitic, with higher pressure the note is dull. The pneumothorax cavity, therefore, obeys the general law, it responds to percussion with its fundamental

12 Martini, P. Studien über Perkussion u. Auskultation, III. Auskultation, Deutsch Arch f klin Med 139 257, 1922

tone until increased tension prevents the vibration of its walls, the tone being of the same, or nearly the same, pitch, so long as it is audible at all. But the note of the normally expanded lung is nontympanitic, the predominating tone is still that fundamental for the air volume, but of the air volume as modified by the peculiar lung structure. The fact that the air space is multilocular does not account for this. For, if a cavity be lightly stuffed with horsehair, shavings, or feathers, so as to divide the air space into numerous small air spaces the note of percussion is still that of the whole air volume. The anatomic structure of the lung does not prevent its air space from vibrating as a whole, because the relaxed lung has a tympanitic resonance, and pieces of lung yield the same resonance which is the higher in pitch the smaller the piece.

If, however, the exenterated lung is blown up to the physiologic degree of tension, the note of percussion is no longer tympanitic, but has the same quality of sound as the normally distended lung. One might draw a parallel between the lung and the pneumothorax cavity, and say that in both cases the loss of tympanitic resonance is due to increase in tension which impairs the vibration of the walls of the resonator. But there is this difference that in the one case the tension of the air, and in the other of the solids, of the cavity is increased. The air of the pneumothorax is under positive tension and, the walls of the resonator being relatively firm and unyielding to distension, the note quickly changes in the direction of dullness as the pressure rises. Whereas, in the normally distended lung, from the nature of the case, during respiration the air pressure cannot rise above that of the atmosphere. When the exenterated lung is inflated so that the air cells are distended, and the tension of their walls approaches the normal tension, the sonority of the note of percussion is increased, rather than diminished, for, a membrane requires to be stretched in order that, as a wall of a resonator, it may vibrate to the best advantage, as is seen in the case of the drum head. If, however, the air pressure is sufficiently increased, the inflated lung becomes dull in the same way as the pneumothorax which is under high positive pressure (Martini).

It may be remarked here that the initial expansion of the lung at birth is effected largely by positive pressure. The accoucheur wishes the child to cry in order that the lung may be well dilated. That is, by straining against a closed glottis or through tense and slightly open vocal cords, the child creates a positive pressure which forces the lung into intimate contact with the walls of the thorax, where it is held thereafter during life by the pressure of the atmosphere.

According to Martini, the acoustic properties of lung tissue are responsible for the pitch of the percussion note. There can be no question, however, that the pitch of that note is not determined by the specific properties of lung tissue as such, but that it is controlled by the

size of the air volume of the thorax just as inevitably as in the tympanic resonance of the pneumothorax cavity. For the pitch of the lung note varies with the size of the lung. It is deep in men, high in women and higher in children. We must suppose therefore that the pitch of the lung and of the larger subdivisions of lung tissue changes constantly during the growth of the child from infancy to manhood or womanhood, under the governing influences of the vibrations of the air volume of the chest. The problem, then, is to determine how it comes to pass that the vibrations of the lung tissue adapt themselves to the dominating vibrations of the air volume of the thoracic cavity.

We have seen that the anatomic structure of the thoracic cage and the manner in which the lung is subdivided into lobes are such as in part to reflect and in part to disperse the vibrations of shocks in order that the hemithoraces may not suffer from the too great violence of vibrations proper to their respective air volumes. It is manifestly necessary that the finer structure of the lung should have a similar protection, that it also should be shielded against too violent proper vibrations of the resonator in which it is situated. And it is also equally desirable that the specific vibrations of its structure shall coincide in periodicity with that of the air volume of the hemithorax. For, if each subdivision of the lung had the fundamental tone of its contained volume of air there would be a different rate of vibration for each subdivision, and there would consequently be strains at the points of juncture of the vibrating bodies. It would be intolerable if a sharp blow, for example, excited vibrations in the part of the lung directly involved which were foreign to the vibrations of adjacent parts of the lung and of the hemithorax as a whole.

The air cells of the lung must necessarily be delicate structures in order to perform their function of aeration. A homogeneous mass of air cells filling the cavity of the hemithorax would vibrate as a whole to imparted concussions, the lung would quiver like a jelly under the slightest shock from the chest wall. But the bronchial tree introduces a heterotropic element. The air tubes are strong and elastic structures filled with air, which from its smaller volume does not vibrate with and therefore to some extent damps the general thoracic vibrations. The bronchi by their disposition and their structure thus tend to reflect a portion of the vibrations which pass through the thorax. The connective tissue envelopes of lobes and lobules primarily form frameworks to strengthen the lung, but also check and tend to reflect vibrations which pass through them. It may be said, then, that the lung from its structure is an organ which is so constituted that, while it is capable of vibrations as a whole, it nevertheless damps and reflects throughout its mass a portion of those vibrations in the same manner, *mutatis mutandis*, as the chest wall. Lung tissue, containing many heterotropic bodies,

vibrates with some difficulty, that is, at a slow rate. This tends to assimilate its periodicity to that of the thoracic cavity, but does not account for the intimate relationship of the two series of vibrations.

Supposing that the bronchi and the fibrous envelopes of the lung were so thick that they reflected nearly all of the vibrations locally at various points throughout its mass. The result would be the division of the lung tissue into subordinate acoustic subdivisions, each of which would vibrate at the rate peculiar to its air volume. These subdivisions would naturally vary in size, and would therefore have different rates of vibration the result of which would be a conflict of vibrations at the juncture of the individual subdivisions, none of which, moreover, would vibrate at the rate peculiar to the lung mass as a whole. Shocks and other vibrations would then produce an irritation at the boundaries of subdivisions and the high rate of vibration of the localized acoustic spaces would be injurious to the contained air cells. The part directly exposed would also bear more than its share of the concussion. Once built too strong there would be no remedy, for irritation could only be countered by proliferation which would make the partitions stronger and thicker than before. Nature's only way, therefore, is to begin with delicate structures and thicken them as the indications arise. The lung of the new-born infant is, we may suppose, adapted at the beginning of its function to its work, from its structure it reflects locally, as well as permits the passage of vibrations, to the proper degree, as determined by the size of the individual thoracic cavity. The facts show that there must be an adaptation of its specific vibratility to the volume of the lung as the latter increases in size during growth.

In full normal respiration the hemithoraces vibrate in resonance as undivided wholes, the sounds of respiration are heard over all portions of the lungs. But in quiet breathing with the upper lobes the breath sounds are faint or inaudible over the lower lobes and, conversely, when the breathing is almost purely diaphragmatic it is difficult to hear it over the upper part of the chest. This must be due to the fact that the vesicular murmur is loudest where the tension of the lung is best for its production. In other words, in such breathing the vibrations of the lung are strongest in its more expanded portions. But the vibrations, though they may not be audible as sound waves, are nevertheless communicated to all portions of the lung. We may fix a line beyond which they are not heard, but in fact there is no line of demarcation because all portions of the resonator vibrate to its fundamental tone and this is of course also true when this tone is called forth by percussion. But this is only true for the reason that the specific vibrations of lung tissue are of the same periodicity as the fundamental tone of the lung. As we saw with regard to percussion it would be a source of irritation if localized breathing produced localized (and therefore higher pitched)

tones. For the best conditions the vibrations of the fundamental tone must shade off through the lung, meeting no foreign vibrations with which to conflict. The problem is the same as in percussion, to make the vibrations of the part equal to those of the whole. The defense against external shock is, of course, operative here, in that the lung tissue vibrates more slowly in proportion to the thickening of tubes and partitions. But in breathing, the vibrations from the larynx are introduced behind all partitions and through all tubes. Strength of partitions and weight of tubes may suffice for the best adaptation to resist external violence, but may not be sufficient for the prevention of a too generalized vibration of lung cells nor for the harmonizing of localized vibrations of parts with the generalized vibrations of the whole lung. If further and more exquisite adaptation is requisite we may think of the tuning as effected on the principle of the weighted string. A string that is weighted vibrates more slowly than an unencumbered string of the same length and size, that is, has a lower tone. In the piano, for example, in order that strings for the deepest tones may not have an inordinate length, the wires are wrapped with smaller wire. As the thorax grows larger, the bronchial tubes and the fibrous partitions increase in thickness in proportion to the increase in size. If in this growth they remain too light, jarring vibrations are a stimulus to greater proliferation. The slight but unending vibrations of the breath sounds are, it may be conjectured, one of the most important of such stimuli. Probably there is no lagging in development, nor ever any marked discrepancy in vibrability between different parts of the lungs as they develop. Rather, the increased weighting of lung tissues, as required for unison of vibrations, takes place *par passu* with the growth, the vibrations of the breath sounds being perhaps the most potent stimulus to a proliferation which in developing the growing tissues shall add just the correct amount of weighting to keep the tissues at the proper pitch, so that all portions of the lung shall always be attuned to the dominating, because most incessant, vibrations to which they are exposed.

Lest it be thought that the expression "tuning" of the lung implies an accuracy like that of the skilled violinist—an accuracy which would seem impossible of attainment under the conditions—it should be remarked that, in view of the difficulty in determining the exact pitch of low tones it is quite possible that the percussion note of acoustic subdivisions of the exentiated lung only approximates the pitch of the fundamental tone. While the fundamental tone of percussion and of vesicular breathing is easily to be distinguished as a tone, the sounds of percussion and of respiration still remain noises which shows that, besides the fundamental tone, various other tones of low pitch are forced on the resonator, its response therefore being with a zone of resonance, not with a single tone. The lack of a clear musical tone and the incon-

larity of curve of the normal thoracic note both in percussion and in respiration, as contrasted with tympanitic resonance, might perhaps be best explained by the persistence of tones which arise from individual acoustic subdivisions. We would think of the process in this way. Each subdivision varying in size from the other subdivisions, in their reflection of a portion of the vibrations which reach them, produce tones of slightly different pitch. But sufficient vibrations pass through the reflecting surfaces to excite the normal response of the thorax by its fundamental tone which, being reinforced to the best advantage, is able to force itself on such of the subdivisions as have a slightly different fundamental tone, but not to the extinction of the latter tones. It is also to be remembered that the optimal expansion of the lung tissue plays a part, as experience shows, in at least the loudness of the vesicular murmur. It is therefore to be expected that, as the lung tension varies during an inspiration in the part of the lung over which the registering apparatus is placed, the strength of the tones resonated by the individual subdivisions will have varying degrees of prominence in the complex.

The lung tissue is protected against the vibrations of voice sounds of higher pitch than that of its fundamental tone by the fact that these are resonated in the bronchi, only the deep notes of a bass voice including the fundamental tone of the thorax. The slowness of these low pitched vibrations prevents injury from too rapid oscillations of lung tissue, but nevertheless the strong vibrations of the lowest pitched organ tones are disagreeable to men whose thoraces respond to such deep tones. What the effect would be if the higher pitched tones of the voice received resonance in the air cells may be inferred from the very unpleasant sensation from "ear piercing" tones, those of or near the fundamental tone of the tympanic cavity, although in the ear the function of the tympanum as a resonator is minimized by its smallness, the irregularity of the cavity and the soft mucous membrane that covers its walls. The intermittency and the wide range of tones of the voice would probably prevent such tones as may be forced on lung tissue from exercising much effect on the lung structure in its acoustic relations.

The fact that, when the glottis is opened wide the chest is silent in respiration, of course overthrows existing theories as to the mode of production of the vesicular murmur by vibrations originating in the lung tissues. Two theories will, however, be referred to briefly, those of Geigel⁹ and of Martini,¹² respectively.

According to Geigel's theory, the vesicular murmur is the sum of the noises of innumerable miniature explosions due to the dilatation of air cells in inspiration and also to the sound of their mutual jostlings as they interfere with one another in their expansion. This theory, as enunciated by Geigel, provides only for the sound of inspiration. To complete the explanation Sahl¹ suggests that the air cells jostle each other also during expiration as they return to their position of rest.

The obvious objections to this theory are first, that the air cells do not collapse in expiration but remain partially filled with air, there can therefore be no tearing apart of adherent surfaces, nothing that resembles an explosion, in inspiration. Second, that the structure of the lung parenchyma gives no support to the idea that air cells jostle one another either in inspiration or in expiration, as if they were a parcel of dried bladders.

According to Martini,¹² the specific vibrations of lung tissue do not appear as the responses of a resonator to the sounding of its fundamental tone but are "of great importance in originating the inspiratory breath sound which is audible over the air bearing lung." He compares the percussion sound with the string of a musical instrument which has been struck, and the vesicular murmur to the sound produced by a string of the same length, the tension of which has been suddenly increased, both methods of exciting the vibrations of the string giving the same tone. Elsewhere he accounts for the persistence of the vesicular murmur in expiration by the fact that a string produces a slight sound when suddenly relaxed. To strengthen this comparison he speaks in both passages referred to of the suddenly expanded or distended lung. But the lung does not as a rule expand suddenly in inspiration. No theory is acceptable which does not account for the presence of the vesicular murmur in slow and easy respiration. The comparison with the struck and tightened strings has the weight only of an analogy. The analogy consists in fact that a stretched string, so long as its length and tension remain unchanged, will always emit a tone of the same pitch whatever excitation may call forth that tone. Each string, in other words, has a fundamental tone depending on its length, just as in general the tone of an organ pipe depends on its length. Martini nowhere gives any indication of the precise mechanism by which the lung would be enabled to produce the sound of the vesicular murmur, further than to state that the lung is brought out of its equilibrium in respiration, and in endeavoring to recover this state of equilibrium vibrates about it periodically and with the same fundamental frequency which is simply the explanation usually given of the production of sound by an elastic body. He furnishes no clue as to the way in which the equilibrium of the lung is disturbed, so as to produce sound in respiration, further than to say that the proper vibrations of the lungs are brought about by the enlargement of the chest in inspiration and its decrease in expiration.

SUMMARY

1 A volume of air confined within elastic walls responds to excitations by a sound, the most important element of which is the tone proper to the dimensions of the cavity. Such cavities may be called resonators in the widest sense of that word.

2 The human thorax is such a resonator. But it differs from other resonators in that it contains solid structures which, when the lung is physiologically active, are under a definite tension.

3 The theories as to the mode of production of the normal vesicular murmur have been unsatisfactory. The proof that the thorax functionates as a resonator is afforded by experiment.

4 Sound may be forced on a resonator in two ways. (1) A somewhat different rate of vibration of the generator may change the fundamental tone of the resonator, it is out of tune, (2) Without alteration of its fundamental tone the resonator may also respond simultaneously to other series of vibrations, its response is a "noise." That the normal sounds of respiration are noises is probably in part due to this cause.

5 Resonators may be excited to the production of the fundamental tone in three ways. (1) The resonator may be struck. An example is the percussion note, (2) A tone of the frequency of the fundamental tone of the resonator may be presented to it for reinforcement. An example is the vesicular murmur, (3) Musical tones of different pitch may be forced on the resonator within a limited range and produce a change in pitch of the fundamental tone. An example is vocal resonance, (4) If the resonator responds strongly to vibrations of, or near, the rate of its normal vibrations, there may be a sympathetic vibration of its walls apparent to the touch. An example is vocal fremitus.

6 The theory of the dependence of the thorax, as a resonator, on sounds produced in the larynx applies only to the relatively weak and slow air currents of *normal* breathing. The phenomena of "reciprocating breathing" show that sound may originate in bronchial tubes through which air is strongly forced.

7 The specific characters of the vesicular murmur are due, not to the generator of the sound, but to the resonator. Any sound produced within the air passages during normal respiratory movements of the thorax may excite what amounts to the vesicular murmur, though the vocal cords are excluded from action by a laryngeal tube.

8 The structure of the thoracic walls and of the lungs is such as to tend both to localize and to disperse the vibrations of impacted shocks.

9 It is necessary that the lung shall be so constructed that the rate of vibration of its parts shall be equal to the rate of vibration of the whole lung, and that the rate of vibration of the latter shall be the same as that of the cavity within which it lies.

10 This requires a constant readaptation of the lung, as it develops within a growing thorax, to the fundamental tone of the cavity.

11 The experiments of Martini have demonstrated a specific rate of vibration of physiologically inflated portions of the lung, which is the

same as that of the whole lung inflated in the same way and does not differ whether the lung be tested within or without the cavity of the hemithorax.

12 Another peculiarity of the human thorax considered as a resonator consists in the fact that it contains a system of smaller resonators—the air tubes, which are more or less perfectly insulated by envelopment with lung parenchyma. This insulation which is thicker in some parts of the lung than it is in others may be impaired or destroyed by disease.

13 The phenomena observed in the physical diagnosis of the diseased lung depend largely on the impairment or destruction of the insulating parenchyma with impairment or loss of its specific vibrability and, consequently, with improved transmission of bronchial sounds.

14 In general, the transmission, not the character of breath sounds is altered in disease.

Book Reviews

A CLINICAL GUIDE TO BEDSIDE EXAMINATION By DR H ELIAS, Dozent and Assistant at the First Medical Clinic of the University of Vienna, DR N JAGIC, Extraordinary Professor and Chief Physician to the Sofienspital, Vienna, DR. A LUGER, Dozent and Assistant at the Second Medical Clinic of the University of Vienna Translated by WILLIAM A BRAMS, M D, Adjunct in Medicine, Michael Reese Hospital, Chicago, Illinois Cloth Price, \$1 50 New York Rebman Company, 1923

As the title suggests, this book is intended as a guide to bedside examination only, no detailed descriptions, theories or procedures requiring laboratory, graphic or other instrumental aid being discussed In short, only such information as can be obtained by the methods of inspection, palpation, percussion and auscultation is given A general schema of a physical examination at the bedside serves as an introduction This is followed by a detailed consideration of each and every portion of the outline It is very comprehensive, and there are no misstatements of fact The authors apparently have made a strong plea for more careful general physical examinations, relying as far as possible on these methods for a diagnosis with the idea of supplementing the information obtained with such adjuncts as the various laboratory tests, graphic records and instruments of precision Greater uniformity and completeness will obtain in the examination itself and the history records by adopting such a schema

THE DIETARY OF HEALTH AND DISEASE By GERTRUDE I THOMAS, Instructor in Dietetics, University of Minnesota Cloth Price, \$2 25 Pp 210, with illustrations and tables Philadelphia and New York Lea and Febiger, 1923

The purpose of this book is to provide an intermediate text as a basis for instruction in schools of nursing or departments of home economics, and is intended for the use of dietitians, nurses and instructors in the sciences that pertain to nutrition A short outline of a course in dietetics is given, and the outline form is used throughout the book The physiology of food in its relation to the human body, the several phases of food chemistry, food preparation and dietotherapy are presented in a very comprehendable yet concise manner The chapters on special diets are exceptionally well written An excellent bibliography is appended to each chapter

CORRECTION

In the article of Drs A W Meyer and F A Cajori, in the May issue, page 581, "F A Cajori, M D," should read "F A Cajori, Ph D"

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